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CARCINOMA OF THE THYROID

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"IN THE ADVANCED STAGES of carcinoma and sarcoma we cannot control the growth of the thyroid. Extirpation of the diseased substance will alone cure the patient from its ravages, but this can only be undertaken in the early stages of the complaint." Thus spoke Allan Burns,[4] in 1811, regarding cases of cancer of the thyroid which he had seen, but he did not mention total extirpation having been performed.

In 1822, Chetuins[7] gave a short but admirable description of the struma scirrhosa. He emphasized the knobby, hard consistency, the strong boring pain, the dyspnea and asphyxia, diffusion with neighboring structures especially the trachea, muscles of the neck, and he closed with the statement: "Finally it is transformed into a carcinoma, a true cancerous growth in which the neighboring nodes of the neck enlarge."

In 1855, Billroth[2] reported a case of thyroid tumor with associated enlargement of the lymph nodes which showed the same variation in morphology as did the thyroid tumor. Billroth was the first to speak of any treatment other than surgery for this condition. He attempted to employ electrocautery by puncture and believed that his patients received symptomatic relief for several days. He was the first to comment on the presence of fetal thyroid disease and goiter.

Cohnheim,[10] in 1876, made one of the first histologic subdivisions for thyroid cancer, and at this time noticed that some of the thyroid cancers resembled closely the normal gland; he used the term "benign metastasizing goiter." Criticism of this term was started by Wolfler,[25] in 1883, and continued until the time of Graham's work, published 50 years later.

Wolfler, in 1883, gave a very clear-cut pathologic classification of thyroid

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cancers similar to that in use to-day. He stated at that time that a typical vascularization is a probable factor in the production of thyroid cancer. The thyroid tissue retains its fetal characteristics until old age and commonly gives rise to atypical epithelium and proliferation of epithelium more than normal tissue. Embryonal masses of epithelium are usually found in the thyroid and, more commonly, in goiters. In these cases he assumed that carcinoma develops if the vascularization either remains atypical or becomes atypical as a result of hemorrhage or venous hyperemia.

In 1902, Ehrhardt[11] reported 200 cases of carcinoma of the thyroid, from which he attempted to draw several conclusions. He stated that in 104 cases a preexisting adenoma was present. In only 21 cases could a preexisting goiter be proved. He believed that degenerative changes, notoriously frequent in old goiters, act as chronic trauma since atypical epithelial growth has been observed in the vicinity of these degenerative changes. This change may be the anatomic expression of the clinically proved relationship between goiter and malignant thyroid.

In 1905, Bloodgood[3] stated there is little or no hope in carcinoma of the thyroid if the operation is performed when the tumor has reached a stage when a clinical diagnosis can be made. Malignant tumors of the thyroid must be removed in the early stage, a period in their growth when they cannot be differentiated from a benign cyst and adenomata. For this reason, every asymmetrical enlargement of the thyroid gland in individuals over 30 years of age should be removed.

Thus, until the twentieth century, time was spent in developing a suitable pathologic classification but rarely was an attempt made to remove these tumors surgically. Enough clinical material had been gathered by 1921 for Wilson[24] to report 21 authenticated cases studied in the United States. He considered that any adenoma of the thyroid composed of embryonal tissue giving histologic evidence of active proliferation is potentially malignant even though it is still contained entirely within the capsule. Wilson was the first to report the results of treatment in 207 cases in which operation alone was performed. Of these 207 cases, 194 were followed and only nine patients lived five or more years after operation.

One of the most useful contributions to our understanding of malignancy of the thyroid gland is the significance of blood vessel invasion, as pointed out by Allen Graham,[14] in 1925. This explained once and for all the paradox of benign metastasizing goiter and also gave for the first time a fairly satisfactory means for selection of those cases which are either actually or potentially malignant and those which are entirely benign. This criterion is not hard and fast, however, as definite blood vessel invasion is found at operation in a number of cases in which no metastasis is found.

The subject of cancer of the thyroid is one that urgently deserves attention, not only on the part of the medical profession, but also by the laity. It deserves this attention and interest because, as will be seen in this discussion, it so often exists first as a benign tumor later becoming malignant, because its removal at this stage or even in an early stage of malignant degeneration

offers such an excellent chance or even possible cure after malignant degeneration has occurred. While the knowledge that many carcinomata of the thyroid originate in discrete adenomata has been repeatedly stressed and is appreciated by a great many physicians, there are still many who either do not realize the possibilities of prevention of carcinoma of the thyroid by removal of these adenomata before they have become malignant, or are not so impressively convinced of this danger that they are willing to advise early prophylactic removal of these tumors. This subject, likewise, deserves attention because there still exists in many physicians' minds an attitude toward this subject which was present, and perhaps justifiable, some years ago but not now—that is, that all cancers of the thyroid were quite hopeless from the point of view of cure.

It is not surprising that individual opinions on this subject should be what they so often are because of the fact that cancer of the thyroid occurs in such a small percentage of patients with goiter that in any individual's practice, unless it be one dealing with patients with goiter in large numbers, an insufficient number of cases will occur to permit him, by actual experience, to obtain information and convictions about the true state of this situation. It is because of the fact that we have had the opportunity of having performed 18,600 goiter operations, and so having had the opportunity to see and manage such a considerable number of patients with malignancy of the thyroid, that we feel obligated to present our experiences with the subject. Since a series of reported cases from a clinic such as ours represents the experiences and results of the combined efforts of surgeons, roentgenologists and pathologists working closely together on cases which have been carefully followed, it permits deductions to be drawn from these not inconsiderable data, the justification of which may be settled and applied to each reader's personal experience with malignancies of the thyroid.

The logical approach to decreasing the number of patients who lose their life from malignancy arising in any given organ is above any other consideration concerned with the removal of premalignant lesions in that organ when such states are known to exist. It seems worth while, therefore, to cite briefly a few illustrative histories out of a large number of malignant degenerations in adenomata which have existed for a considerable period of time without evidences of malignancy. In these cases, it can with quite reasonable safety be stated that for at least a definite period of time the adenomata were not malignant and their removal during this period would quite probably have resulted in the prevention of malignancy.

ILLUSTRATIVE CASE REPORTS

Case 1.—A female, age 20, came to the clinic June 23, 1937, because of enlargement of the neck for the past three or four years. It had been known to her medical advisers that this enlargement was due to a palpable, discrete adenoma of the thyroid. She had been advised that since it had given her no trouble it should not be removed.

Examination revealed a very moderate, smooth enlargement of both lobes of the thyroid gland. A firm, smooth, round adenoma the size of an English walnut could be felt in the left lower pole extending beneath the sternum. Roentgenograms of the

trachea showed a soft tissue mass to the left and anterior to the trachea, displacing it to the right and compressing it anteroposteriorly. It is to be noted that this patient and her physicians knew that she had had this adenoma for three years but she had been wrongly advised to do nothing about it until it bothered her.

On June 25, 1937, partial thyroidectomy and wide removal of the adenoma were performed. The pathologist's report was carcinoma, partly papillary, partly small cell type. The patient was discharged July 23, 1937.

Roentgenotherapy was begun July 6. A series of 23 treatments was given; 7,000 r units were delivered to the thyroid region. There was an extremely severe postradiation reaction to combat, in which quite aggressive measures were necessary.

The patient married and remained well until March, 1939. She returned March 24, 1939, because of headaches for the previous three weeks. The headaches were frontal in type and came on at any time of the day or night. She had had no difficulty with the neck. There was no sign of local recurrence and her general condition was quite satisfactory. Roentgenograms of the accessory sinuses showed them to be well developed and apparently clear.

On May 1, 1939, right cerebral craniotomy was performed by Doctor Horrax of the Neurosurgical Section in the clinic, with excision of a suspicious area in the postfrontal region, decompression for extreme edema and removal of bone flap. The diagnosis was metastasis from the thyroid carcinoma. The patient died May 17, 1939.

Without intending to be specifically critical of her medical advisers but solely for the purpose of presenting the case as a lesson, the deduction from this history is sad but clear and unmistakable. Had this young lady had her small adenoma of the thyroid removed three years previously when it first appeared she would in all probability be alive and well to-day.

Case 2.—A male, age 24, came to the clinic January 31, 1935, because of a "goiter" of ten months' duration. There had been little or no change in the size of the neck during this period. No symptoms were present and the patient felt physically fit.

Examination revealed the left lobe and isthmus of the thyroid gland to be enlarged to four times normal size by the presence of a discrete, movable thyroid adenoma. The trachea was deviated to the right in the lower cervical region. Since there was no hyperthyroidism present in this case it was with difficulty that this young man and his parents were persuaded regarding the wisdom of removing it. It was only when the general danger of malignancy in all thyroid adenomata was stressed that operation was even considered. This patient strenuously resisted immediate operation because of a desire to complete an already begun important year of graduate study.

On February 11, 1935, a discrete adenoma, approximately 6.5 cm. in diameter, was removed from the left lobe. The pathologist's diagnosis was papillary adenocarcinoma. The patient was discharged February 16, 1935.

A series of 12 roentgen ray treatments were given, directed to both sides of the neck through two portals.

The patient has remained well to date and there is no evidence of recurrence.

In this case there is also a lesson. Had this patient had his adenoma removed ten months previous to the time when he did, he might well have escaped malignancy. Had he been permitted to complete his year of graduate study he might well have lost his life.

Case 3.—A female, age 31, came to the clinic January 30, 1935, because of swelling of the neck for two years. Examination revealed two discrete adenomata the size of English walnuts in the upper pole of the right lobe and a single small adenoma in the left lobe. This patient and her husband were strongly opposed to any operative procedure. The thyroid tumors were not of sufficient size to make them visible. They

caused no pressure. There was no toxicity and they had been advised against removal by their attending medical adviser.

At operation, February 6, 1935, two adenomata of the right lobe were found and the lobe was enlarged one and one-half times its normal size. There was a single adenoma in the upper pole of the left lobe. A right subtotal hemithyroidectomy with removal of the adenomata and excision of the adenoma of the left lobe was performed. The pathologic diagnosis was papillary adenocarcinoma. She was discharged February 15, 1935.

A series of 11 roentgen ray treatments, of 300 r each, was given, delivered through two portals. A fairly marked skin reaction occurred following the treatments.

The patient has remained well and there is no evidence of recurrence.

Again, in this case, this patient had been assured repeatedly that the enlargement in her thyroid was harmless and did not require attention. It was only when the aid of her uncle, who was a physician, was enlisted that she could be persuaded to have the operation performed. No one can deny the fact that the removal of these adenomata two years earlier would have been wiser.

Case 4.—A female, age 67, first came to the clinic with her attending surgeon because of a disagreement on the part of her physician and her surgeon as to whether or not she should be operated upon for possible gallstones. It had been known for some years that she had a discrete adenoma of the thyroid. After examination at the clinic, it was advised and accepted that she did not have gallbladder disease and should not have any operation for it, but removal of the adenoma in her thyroid gland was strongly advised. While her physician and her surgeon were divided in their opinion concerning operation upon her for gallstones they were positively united in opposing any operation upon a single adenoma of the thyroid which had been present without symptoms for many years, and it was only when the responsibility for possible, though unsuspected, carcinoma was placed upon the patient and her physician and surgeon that it was accepted.

This unruptured adenoma was removed; it was considerably substernal. The pathologist's report was adenocarcinoma. Roentgenotherapy was given to the region of the thyroid gland.

While the patient has remained well, it, undoubtedly, would have been better to have removed this adenoma as a prophylactic measure earlier, and had further delay resulted an unnecessary fatality would undoubtedly have occurred.

These typical examples represent but a few of a large number of our cases of malignancy of the thyroid in which, from the history and the pathologic findings, it could be assumed that a benign adenoma of the thyroid had been present for some time, the removal of which, in this stage, would have permitted the individual to have escaped the resulting risk to his life and intensive postoperative radiation, with its necessarily associated roentgen ray sickness and the unavoidable and disfiguring skin changes associated with massive high voltage roentgen radiation. Numerous examples similar to the first case, in which it can be reasonably assumed that the patient lost her life needlessly, occur in our records and could be reported in considerable numbers but would serve no purpose other than to undesirably present criticism of the lack of knowledge concerning malignant changes in adenomata of the thyroid on the part of patients and their advisers.

Clinical Diagnosis of Malignancy of the Thyroid.—While it will

be impossible in many cases without biopsy to settle with certainty the absolute presence of malignancy and its type, which is of particular importance from the point of view of prognosis and the justification of prolonged and intense roentgenotherapy, it will be of value to discuss from the point of view of a surgeon who has examined many of these cases preoperatively the features which suggest the possible presence of malignancy in the thyroid and the conditions with which they may be confused.

The thyroid state which will most often cause the observer, with but little experience in palpating thyroid glands, to consider wrongly the possible presence of malignancy of the thyroid is that of thyroiditis. When the thyroid gland is chronically inflamed and occupied by round cell infiltration, as it is in this state, it assumes such a condition of stony hardness as to resemble that condition which one sees so frequently associated with malignancy anywhere and particularly in the thyroid. The distinguishing diagnostic point about thyroiditis as compared with carcinoma of the thyroid is that it is a diffusely infiltrating process, pervading the entire gland or one lobe of the gland and causing but moderate and symmetrical general enlargement.

The outstanding clinical diagnostic feature of thyroiditis is that while the gland may take on a hardness of almost marble-like consistency its symmetry and anatomic outline remain in general unchanged. This is quite in contradistinction to what one finds in malignancy of the thyroid. Since malignancy of the thyroid usually arises first locally, the symmetry of the gland is frequently lost. Local enlargement of the gland occurs and distinguishable firmness in the palpated lesion usually does not occur until the malignancy is quite well advanced. The association of enlarged adjacent cervical lymph nodes with any indurated swelling of the thyroid should make one very suspicious of thyroid malignancy.

The feature indicating possible malignant degeneration of an adenoma of the thyroid, which has existed for some time, is a change in consistency from one of moderate firmness to one of induration. The two common causes of a change in consistency to one of unusual firmness in an adenoma of the thyroid are the occurrence of malignant degeneration within the adenoma and hemorrhage into the adenoma. The former occurs gradually and without pain and localized tenderness. The latter occurs in a quite short period of time and is usually associated with pain and localized tenderness in the adenoma. When in a discrete adenoma or adenomata, which have existed for some time with well defined and palpable outlines, a loss of this sharply defined outline with diffusion of the firm tumor mass into the parenchyma of the gland occurs, one should be suspicious that malignant degeneration has taken place inside the adenoma, eroding through the capsule, involving the parenchyma and so causing to be lost the discrete outline of the unruptured discrete thyroid adenoma (Fig. 1). When a discrete adenoma or discrete adenomata of the thyroid have existed for some time as quite movable tumors, and have then become fixed to the surrounding structures, one should be suspicious that this fixation is caused by malignant degeneration within the adenoma, erosion of the capsule and invasion of adjacent tissues, thus

causing the fixation. While the reactions about a thyroid adenoma secondary to hemorrhage into the tumor produce some degree of fixation, this is far less definite than is the fixation caused by malignant degeneration within the adenoma. The firm attachment of the prethyroid muscles to any firm tumor felt at the time of operation is extremely suspicious evidence of the probability that the firmness and the attachment of the thyroid tumor to the muscles are the result of malignant degeneration within the adenoma. When at operation, with the separation of the prethyroid muscles from the anterior surface of an indurated thyroid gland, bits of the thyroid come away from the in-

FIG. 1.—Adenoma of the thyroid with malignant change, showing erosion of the capsule.

durated gland adherent to the muscles, this is quite suggestive evidence that the lesion is malignant and has already infiltrated into these muscles. Voice changes due to recurrent laryngeal paralysis secondary to involvement of the nerve in malignancy occasionally occur, but extensive malignancy of the thyroid can so often occur without producing this paralysis that this feature has but little value as a sign indicating the possible presence of malignancy in the thyroid.

Up to the time that we had had a considerable experience with malignant degeneration in adenoma of the thyroid, we had assumed two attitudes which we now know were not proper ones. One was that there was little likelihood that malignant degeneration would occur in a very small thyroid adenoma and the other, that there was but little, if any, danger of a thyroid adenoma becoming malignant in a young person. In Figure 2 may be seen an adenocarcinoma occurring in an adenoma the size of one's thumbnail; and this has occurred several times in our experience. Malignancy of the thyroid has

now occurred in our experience in so many young people that we know that dependence upon youthfulness in patients with adenomata of the thyroid as a protection against possible malignant degenerations is not advisable.

While there is a lack of appreciation and aggressive surgical action in the matter of malignant degeneration in adenomata of the thyroid, there is also an almost universal lack of knowledge in the minds of most physicians and many surgeons concerning the existence of, the diagnostic features of, and the proper management of the sometimes already malignant and in all cases potentially malignant lesions associated with the occurrence of lateral aberrant thyroid masses.

The thyroid gland in intra-uterine life arises at a point in the fetus, indicated in later life by the foramen caecum, at the apex of the circumvalate papillae on the back of the tongue. It is at this point at which the thyroglossal duct, then connected with the thyroid, empties. With increase in size of the fetus, the thyroid gland descends from its place on the back of the tongue to its position on the tracheal rings, leaving along its course of descent the thyroglossal tract which normally becomes completely obliterated. When failure of obliteration occurs a thyroglossal cyst is then formed. Occasionally thyroids fail to descend into their position in the neck and then the so-called lingual thyroid occurs, three examples of which we have had in our experience.

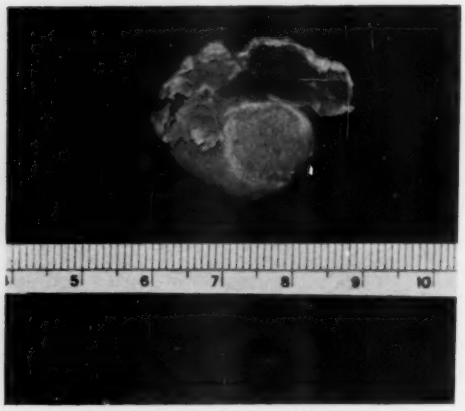


FIG. 2.—Portion of the thyroid with a small adenoma in which adenocarcinoma is present.

While the true origin of the thyroid is from this central anlage, there occasionally arise laterally from one or both sides of the neck papilliferous glandular masses from the ultimobranchial bodies which are known as lateral aberrant thyroids. These aberrant thyroid structures occur up and down the neck just in front of and under the edge of the sternocleidomastoid muscle. They are discrete, gland-like masses varying in size and consistency with the length of time which they have existed. In their early stage, they closely resemble enlarged lymph nodes and are often mistaken for them. They are in the beginning soft, freely movable and discrete, and do not tend to mat together. They cause no symptoms whatever when they first appear and are often thought by those who have not had experience with them to be inflamed cervical lymph nodes. These lateral aberrant thyroid masses frequently occur with a coexisting similar papilliferous nodule within the thyroid gland itself which may represent a metastasis of these lateral thyroid bodies into the thyroid gland. This situation can and has led to the removal of one of the gland-like masses or the nodule in the thyroid and its submission to a patholo-

gist. If it be one of the lateral gland-like structures and the report that comes back from a pathologist is simply malignancy without qualification, the assumption has been, in cases operated upon elsewhere and with which we have dealt, that the tumor in the thyroid is malignant and the lateral gland-like masses in the neck are metastases. If the tumor in the thyroid is removed first and this pathologic report is returned, then the same improper interpretation of the situation can occur. Both of these experiences have occurred in our practice in patients later sent to us for operation, when the true state of affairs had been settled. It is important to realize the necessity of complete dissection of both sides of the neck, together with wide removal of any tumors within the thyroid itself, when these lateral aberrant thyroid bodies exist.

In such a situation as is above described, we have had patients sent to us in whom upon removal elsewhere of the papilliferous nodule in the thyroid and a report of malignancy of the thyroid returned, without specifying the type by a pathologist without considerable experience with thyroid disease, it was assumed that what in reality were lateral aberrant thyroid bodies were metastases to the lymph nodes and that the case was hopeless. In such cases it has been assumed that further operative procedures were not indicated because of the hopelessness of the situation in view of the metastatic nodules in the lymph nodes.

Such a situation would, of course, never occur in the hands of a surgeon or a pathologist who had had any considerable experience with thyroid states. It does, and has, in our experience occurred several times in the hands of men who have not had considerable thyroid experience, and with no purpose of criticism but rather to impress upon all the need to have in mind the possible presence of the lateral aberrant thyroid bodies and their potential malignancy, it is cited. To give patients, having these lateral aberrant thyroid masses with or without thyroid implantations, the best chance both sides of the neck should be thoroughly dissected from the clavicles to the mastoids with complete removal of all aberrant thyroid tissue together with any nodules in the thyroid gland itself. We have had 36 cases of malignancy of the lateral aberrant thyroid bodies in which operation was performed, and two patients have died of recurrence.

The most satisfactory management of thyroid malignancy to-day is by means of a combination of radiation and surgery, as is shown in Table I by

TABLE I

CARCINOMA OF THE THYROID

Five-Year Survival Rate, 231 Cases

	Per Cent
Adenoma with blood vessel invasion	71
Papillary cystadenoma, malignant	62
Papillary adenocarcinoma	80
Alveolar adenocarcinoma	27
Small cell carcinoma	22
Giant cell carcinoma	17
Fibrosarcoma	33

the five-year survival figures in patients treated by surgery and radiation. Surgery finds its most satisfactory place, of course: First in the prophylactic removal, while the tumor is still benign, of the discrete tumors of the thyroid in which malignancy may later arise. It finds its next most satisfactory application in those tumors in which malignancy exists within the capsule of such an adenoma but without erosion or invasion of the capsule. Its next most satisfactory application is in those cases in which malignancy has occurred within the adenoma, has eroded the capsule and involved the parenchyma of the thyroid at only one point, so that relatively complete removal of the malignancy can be accomplished. Its least satisfactory application will, of course, be in those cases with wide infiltration of muscle, trachea and lymph nodes by the infiltrating thyroid growth.

As the result of this quite extensive operative experience with thyroid malignancy, we have, with our successes and failures, acquired quite definite convictions concerning the employment of surgery in thyroid malignancy.

We believe that it is wise, even in advanced thyroid malignancies, to obtain a biopsy specimen for pathologic examination, since the degree of radiosensitivity is known to vary so much with the different types of thyroid carcinoma. We have, as have many other men interested in thyroid malignancy, had cases with extensive and seemingly hopeless thyroid malignancy which when of the radiosensitive type, under radiation, have become discrete, movable and removable. We have seen their metastases controlled by radiation and have seen them with repeated radiation and local removal live many years, to die of entirely other causes than their thyroid malignancy. One of many examples is the case of a woman who recently died here of coronary thrombosis. Seven and one-half years ago she appeared in the clinic with extensive, seemingly hopeless, malignant papillary cystadenoma of the thyroid, with multiple fixed masses and metastasis to the cervical lymph nodes. Under radiation these masses became mobile and discrete, were removed, and the metastases were controlled by roentgen ray. When she died, at the end of seven and one-half years, of a cardiac lesion there were still multiple cicatricial nodules present but she had remained entirely well and had lived a normal life during this time.

One must not fail to realize because of the capacity of thyroid malignancy to vary widely in type, to vary widely in its capacity for distant metastases and particularly to vary greatly in its degree of radiosensitivity, that it is in all cases of the first importance to know the type of malignant thyroid tumor one is dealing with. This will influence one as to how much surgery to apply and will distinctly influence one as to how much radiation to apply.

In hopeful tumors, it will be justifiable to employ radiation dosages which may seriously upset the patient's general condition and, likewise, one may justifiably employ dosages which will result in permanent skin changes.

It is not easy to set down upon paper in what cases to apply surgery in patients with cancer of the thyroid, and it is particularly difficult to set down how much to do when it is applied. In this experience with these malignant

lesions of the thyroid, we have dealt with almost every variety of problem. While we have learned a great deal about what to do surgically with these cases, we have learned even more about what not to do in these cases. I know of no group of cases where judgment and experience pay higher dividends than in the decisions in these cases to withhold surgery entirely, to undertake complete radical removals, and to stop and give up any ideas of radical removals after once undertaken.

In the patient with a discrete adenoma with an unruptured capsule, even though the tumor be of such firm consistency that malignancy is suspected, it is in our opinion unnecessary to do more than complete removal of the adenoma with its capsule intact. It is unnecessary and unwise in this situation to undertake complete thyroidectomy together with removal of the thyroid adenoma. If, however, the malignancy has eroded the fibrous capsule of the adenoma and involved the parenchyma of one lobe of the thyroid it is important in such cases that the entire lobe and isthmus with the contained malignancy be removed intact. Provided the carcinomatous adenoma has involved but one lobe, it is unnecessary to perform a total thyroidectomy and remove the unaffected lobe. If recurrence is to take place at this stage, it is most likely to be in the lymph nodes and is best controlled by irradiation.

If carcinoma has involved the entire gland an attempt may be made to remove it by removing the entire thyroid gland with its contained malignancy, if the involved gland appears movable. Attempts may be made to remove such glands even when they are quite fixed, provided there is not fixed and infiltrating carcinomatous tissue *extending below the clavicles and into the mediastinum.*

It is important in the surgery of cancer of the thyroid to realize that the trachea with its cartilaginous rings and the fibrous sheath which envelops it are quite resistant to carcinomatous infiltration. In late malignant lesions of the thyroid one will at times find the cartilaginous rings of the trachea softened, at times collapsed, and at times the tracheal wall actually invaded. In many cases, however, which seem so fixed to the trachea that malignant infiltration seems certain, operative investigation will demonstrate that the fixation is due to a cicatricial layer of condensed connective tissue between the back of the malignant thyroid and the trachea without infiltration and permitting clean and complete removal of the thyroid gland.

In occasional cases the carcinomatous process so remains within the thyroid gland itself that extension to trachea and muscles does not occur, permitting easy and complete ablation of the entire thyroid. Even when the malignancy so involves the thyroid that there is firm fixation to the trachea one may explore the gland for its possible removal.

With the exception of the patient with a relatively benign and early papillary cystadenoma in an unruptured adenoma, it is our opinion that malignancy of the thyroid should never be treated by surgery alone but in combination with irradiation. There are many patients with advanced malignant lesions of the thyroid in which no operation should be undertaken other than that

of obtaining a biopsy specimen to settle its type and so its amount of radiation. In most patients with carcinomata of the thyroid too advanced for

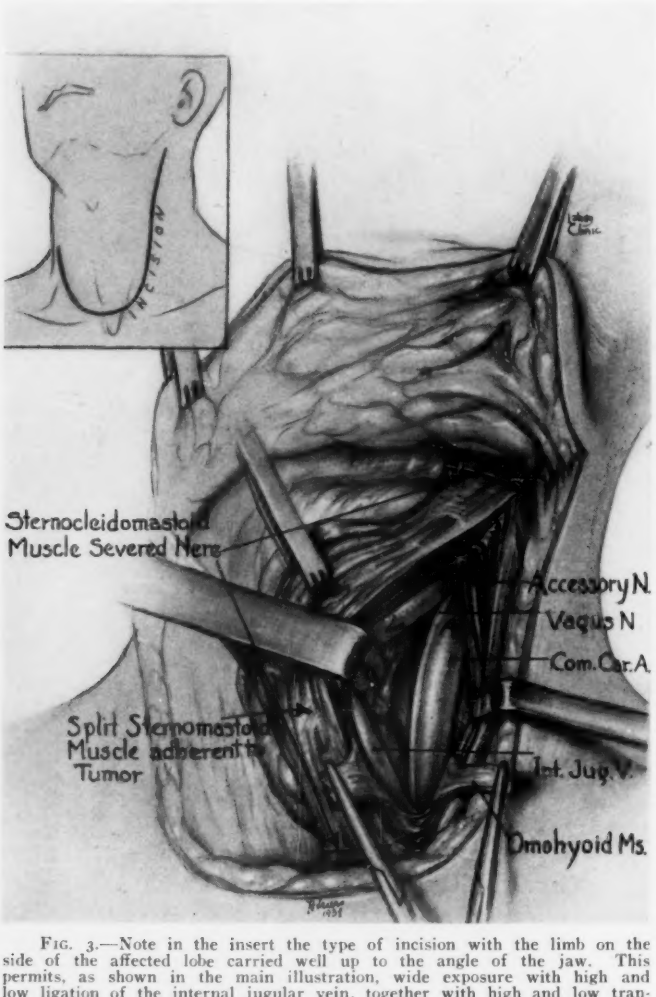


FIG. 3.—Note in the insert the type of incision with the limb on the side of the affected lobe carried well up to the angle of the jaw. This permits, as shown in the main illustration, wide exposure with high and low ligation of the internal jugular vein, together with high and low transection of the sternomastoid muscle. It is possible with this exposure to remove the lobe involved by the malignancy with adjacent lymph nodes, with most of the sternocleidomastoid muscle and all of the section of the internal jugular vein locally related to the thyroid malignancy. Since malignancy of the thyroid gland is so apt to extend along venous channels this is important as it removes, unopened, those venous channels connecting with the internal jugular, the superior, middle and inferior thyroid veins along which malignancy tends to spread. Note that a small strip of sternocleidomastoid muscle is left at the back, that the internal jugular vein has been separated from the common carotid artery and the vagus nerve, thus establishing the cleavage line which is to represent the outer limit of the blocked-out area to be removed. Note the dotted lines which mark the points above and below at which the sternomastoid muscle and internal jugular vein are to be severed, establishing the upper limits of blocked-out area for removal.

removal, there will be metastasis to the lymph nodes. The removal for biopsy of such a discrete and movable lymph node, often under local anesthesia, is a much easier and safer procedure than the exposure for biopsy of the infil-

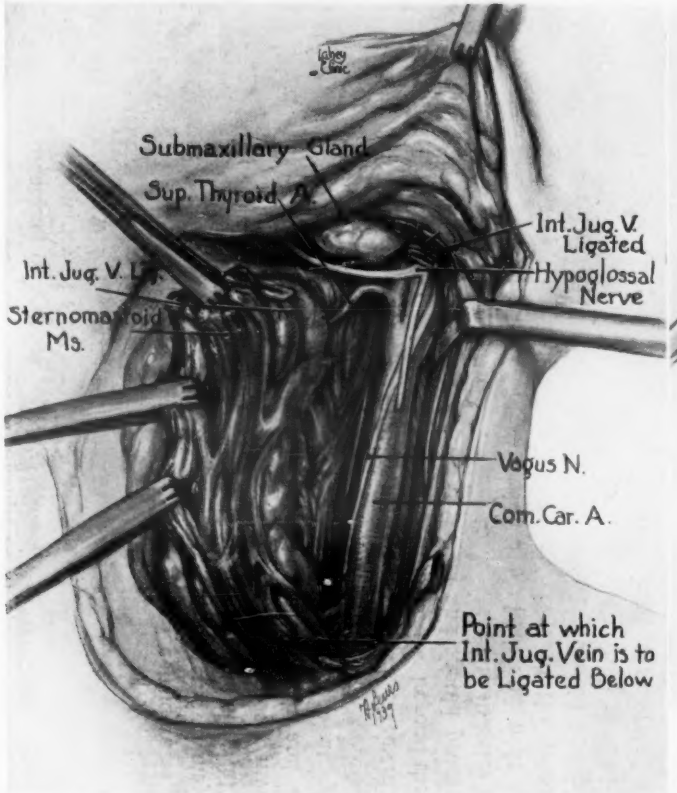


FIG. 4.—Illustrating the further development of the block removal of one lobe of the thyroid gland involved in malignancy, the sternocleidomastoid muscle and the entire neck segment of the internal jugular vein. In this illustration the upper segment of the sternomastoid muscle has been severed, the internal jugular vein has been severed high between two ties and the upper portion of the block turned inward. The anatomic structures encountered are plainly shown and labeled so that they require no comment.

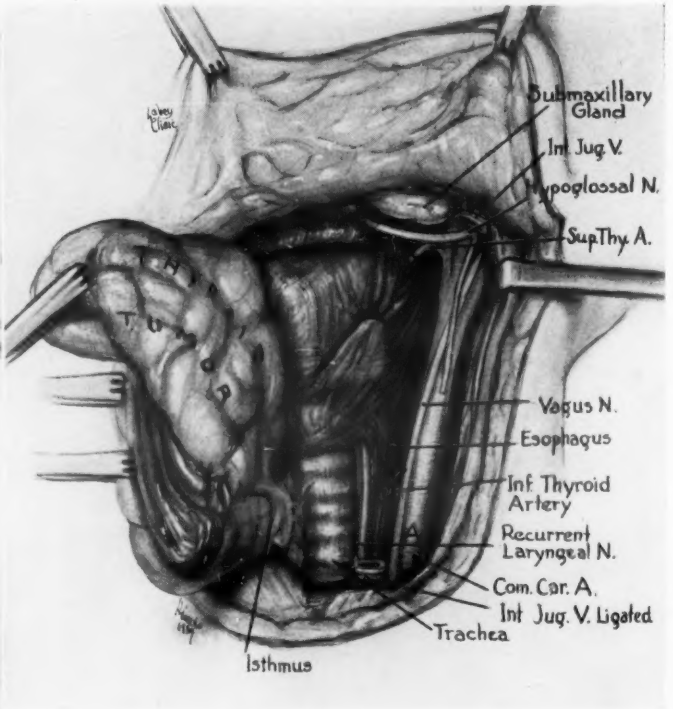


FIG. 5.—In this illustration the dissected block has been entirely freed and turned toward the median line so that it is attached to the remaining lobe of the thyroid gland by the thyroid isthmus which has been freed from the trachea. The sternomastoid muscle has been severed at its lowest point and the internal jugular vein has likewise been cut between ligatures at its lowest point in the neck. The recurrent laryngeal nerve is shown preserved as in the actual operative procedure. It was possible to separate and save the nerve without leaving behind obviously malignant tissue. It will frequently be possible to do this. Note that the descending branch of the hypoglossal nerve has been cut since the muscles which it supplies have been removed.

trated thyroid with the consequent bleeding and in a patient so obstructed in respiration that any anesthetic or manipulation on his neck may further add to his breathing difficulties.

When malignancy of the thyroid has ruptured the capsule of the adenoma of the thyroid in which it started, when it has involved the surrounding thyroid parenchyma and when it has extended beyond the thyroid gland and involved the lateral and overlying muscles even with considerable fixation, provided the process is limited to one side of the neck, removal may still be attempted, not with any idea that it will accomplish complete surgical removal and a surgical cure, but to eliminate all of the tissue grossly involved in the malignancy. This gives irradiation less to accomplish and often so removes pressure from the trachea that complete relief of respiratory obstruction may be accomplished.

If radical surgical removal of an extensive unilateral carcinoma of the thyroid, in such a case as described above, with infiltration beyond the thyroid is attempted, the removal should really be radical and should proceed along definite lines. No attempt should be made to separate the muscles over the thyroid as in conventional thyroid operations. A high and wide skin flap should be turned up, leaving the platysma adherent to the front of the malignant gland (Fig. 3). The internal jugular vein should be ligated just above the clavicle and just below the mastoid. The vein is severed at these points between the ties and the entire internal jugular separated from the common carotid artery and vagus nerve in the carotid sheath and left attached by its branches, superior, middle and inferior thyroid veins, to the malignant thyroid (Fig. 4). If there be any extension into the muscles, the sternomastoid should be severed above and below and turned inward with the internal jugular vein and the malignant lobe of the thyroid. The superior and inferior thyroid arteries are tied and severed, and the entire lobe of the thyroid gland, with its contained malignancy, with the internal jugular vein attached to it and, if necessary, also with the sternomastoid muscle, is turned up and dissected inward until it is completely freed from the trachea and until the thyroid tissue in the remaining lobe is reached (Fig. 5). In cases sufficiently extensive so that this radical procedure is justified, it is usually unwise to attempt dissection and preservation of the recurrent nerve although, even with quite extensive involvement of one lobe of the thyroid with malignancy, it will be found possible to dissect and preserve the nerve without limiting the radicalness and completeness of the removal of the carcinomatous lobe. One must realize in all operations for extensive thyroid malignancy that wide and complete removals of all tissue involved in the malignancy will not be possible.

The removal of the internal jugular, together with the malignant lobe of the thyroid, is of great importance in the surgical management of these cases due to the fact that thyroid malignancy so tends to extend into the veins and along their course. If the internal jugular be ligated and severed high and low in the neck then not only can the jugular itself be removed with the

malignant glands but also all the tributary veins, running from the thyroid into the section of the jugular which is removed, superior, middle and inferior thyroid veins can be removed. The tendency for recurrent thyroid malignancy to extend within the thyroid veins and the need for wide and radical removal of the adjacent veins together with the tumor in these cases, have been well stressed by Dr. Allen Graham. It is, likewise, important that this same principle be employed in the surgical management of recurrent thyroid malignancy.

In the surgical management of these malignant lesions of the thyroid, we have learned that it is unwise to continue attempting to remove malignant thyroids unless the dissections can be carried along definite anatomic lines of cleavage. If it is found that the malignant mass has, for example, grown into and fused with the trachea, it is better to give up any attempt at removing it than to attempt to cut away segments of its malignancy. It is particularly dangerous to attempt to remove masses of thyroid malignancy which have extended below the clavicles into the mediastinum. Extensions of thyroid malignancy from the lower poles into the mediastinum do so by infiltrating diffusely into mediastinal tissue and without establishing any definite lines of cleavage that permit safe separation and removal. Attempts to remove mediastinal extensions of thyroid malignancy result only in profuse venous hemorrhage with the postoperative occurrence of hematomata here that further embarrass respiration and permit the development of mediastinal infection. It is extremely important to appreciate that thyroid malignancy tends to extend backward in the neck into the groove between the trachea and the esophagus and that the esophagus is very prone to become attached to the malignant thyroid tissue often without actually being involved in it. As the malignant thyroid lobe is rolled inward for dissection, the malignant thyroid lobe often pulls up with it the attached esophagus. Many times we have had to carefully separate the pulled up and adherent esophagus from the malignant thyroid lobe before the lobe could be resected. Unless the thyroid malignancy has actually invaded the wall of the esophagus, that structure can readily be dissected away from the malignancy and permitted to fall back into its normal location. This is an extremely important point as the adherent esophagus can very easily be overlooked and injured. When adequate operations for malignancy of the thyroid have been completed, the trachea will be quite bare since all of the lateral lobe and isthmus will have been removed. There will, however, be instances in which, because of fusion of the growth with the trachea, it will not be possible to remove all of the tissue from over the trachea. In such cases, care must be taken to expose and clean off the trachea thoroughly, below the isthmus when it is possible, against the possibility that with postoperative swelling, edema and hematomata, the need for a tracheotomy may quickly and urgently arise. The time to prepare for a tracheotomy in any thyroid operation and particularly in thyroid operations for malignancy is when the first operation is being performed, when there is good exposure, free breathing and when with a satisfactory unhurried dissec-

tion the trachea can be freed and exposed in a dry field. If when the operation for thyroid malignancy is completed there is the slightest question about the patient's breathing, the tracheotomy should be performed then and not later after the patient has suffered from hampered respiration and suboxygenation for some time. It will frequently be necessary to perform temporary tracheotomies in patients with extensive carcinomata of the thyroid who have had extensive dissections of the trachea.

TABLE II

PATHOLOGIC GROUPING OF MALIGNANT TUMORS OF THE THYROID*

Group I: Low or Potential Malignancy
- (1) Adenoma with blood vessel invasion
- (2) Papillary cystadenoma with blood vessel invasion
  - (a) Originating from thyroid
  - (b) Originating from aberrant thyroid

Group II: Moderate Malignancy
- (1) Papillary adenocarcinoma
- (2) Alveolar adenocarcinoma
- (3) Hürthle cell adenocarcinoma

Group III: High Malignancy
- (1) Small cell carcinoma (carcinoma simplex)
  - (a) Compact type
  - (b) Diffuse type
- (2) Giant cell carcinoma
- (3) Epidermoid carcinoma
- (4) Fibrosarcoma
- (5) Lymphoma

PATHOLOGY.—The term "adenoma of the thyroid" has so frequently been misapplied to mere nodular aggregates of thyroid tissue that its present connotation is very indefinite. We regard as adenomata only those masses of thyroid tissue that can be considered definitely neoplastic. Certain of the tumors formerly regarded as adenomata would now be excluded and considered as foci of involutional change. For a true adenoma we require the following criteria to be fulfilled:

(1) Complete encapsulation.
(2) Homogeneous texture, grossly and microscopically, throughout, with the exception of degenerative foci such as cysts, calcification, or fibrosis.
(3) Distinct variation of the tissue within the capsule from that outside.
(4) Evidence of compression of adjacent thyroid tissue by the nodules.

We classify adenomata in four major groups, according to their histologic appearance: The embryonal adenoma is the least differentiated, made up of solid columns of small, compact, polyhedral, usually intensely basophilic cells, with varying amounts of a rather loose, edematous stroma. These resemble

* Modified from an earlier classification from this clinic.[8, 9]

the structure of the thyroid gland in the earlier stages of embryonic life. The fetal adenoma is a somewhat more differentiated type, where there may be some small clusters of cells, but, in addition, there are some follicles containing a small amount of a rather thin, watery colloid. Again, the stroma is fairly abundant and edematous.

In the simple adenoma, the structure more nearly mimics that of the normal thyroid gland, although it does not show the same degree of functional activity as does the adjacent normal thyroid tissue. Very rarely a true toxic adenoma may be discovered, in which there is hyperplasia and hyperfunction by the tissue of the adenoma itself and not as a result of the surrounding thyroid tissue. The bulk of the so-called toxic adenomata is composed of either nodules in an endemic goiter showing secondary hyperplasia or else true adenomata occurring in an hyperplastic gland. A subtype of adenoma, rarest of all, is the so-called Hürthle cell adenoma,[12] or as it is sometimes spoken of, the Getzowa adenoma. This is characterized by the presence of acini lined by large, pale, clear, acidophilic cells, with rather large, prominent, vesicular nuclei. These range from high cuboidal to columnar and are generally clearly demarcated from one another. Occasionally, they occur in masses or strands, but, in general, alveolar formation is fairly distinct.

The colloid adenoma is the most differentiated and one of the rare forms of tumor, where the acini are all greatly distended by huge aggregations of colloid. The epithelium is usually low cuboidal or flat. These may be occasionally mistaken for foci of hyperinvolution.

Any one of these types of adenomata may become malignant. Practically all have thin-walled blood vessels, and, as has been so clearly pointed out by Graham,[13] one of the best evidences of malignancy in these tumors is the existence of blood vascular invasion.[11] Less than 3 per cent of adenomata show blood vessel invasion, and of those that show it, only 10 per cent show definite clinical evidence of malignancy. However, it is impossible to differentiate the small percentage of those adenomata with blood vessel invasion that do recur or metastasize from those that make no further trouble. Consequently, it is necessary to consider the whole group of adenomata with blood vessel invasion as potentially malignant, even though we recognize that 90 per cent will cause no further trouble. Undoubtedly, several factors are of importance here: The extent of the vascular invasion; the compactness of the growth, determining the ease with which emboli may form, and the site in which emboli may lodge.

The metastases of adenoma with blood vessel invasion vary in appearance; some are undifferentiated (Fig. 6), others histologically indistinguishable from normal thyroid tissue. The commonest metastatic sites are the bones. The existence of bony metastases is not incompatible with long life, one patient seen having lived for seven years after a pathologic fracture called attention to the existence of the bony metastases. Those cases which show

gross evidence of blood vessel invasion are much more apt to show definite clinical evidence of malignancy than those with only microscopic evidence.

It is important in determining the presence of blood vessel invasion to rule out artefact, whereby acini may seem to lodge within the lumina of vessels. We prefer to accept as definite evidence of blood vessel invasion only those cases in which actual penetration of the vessel wall may be made out. That such invasion must occur rather widely in these tumors is shown by the fact that the sections studied represent only a small fraction of the total mass of the tumor. So far, only one questionable case has been encountered where the usual routine examination of sections of the adenoma failed to disclose blood vessel invasion and subsequent development of metastases

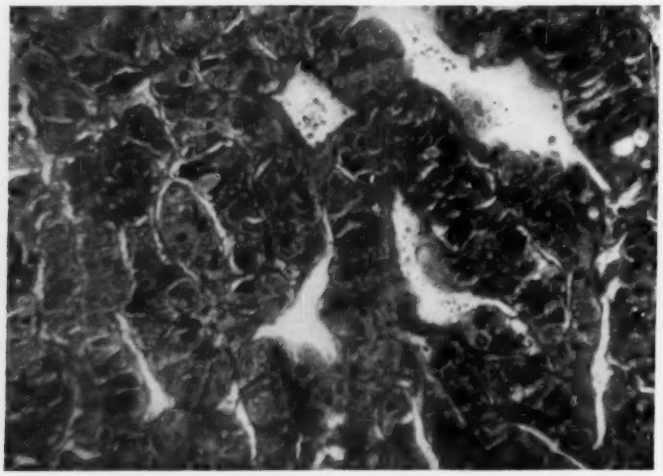


FIG. 6.—Embryonal adenoma of the thyroid showing undifferentiated cells and marked vascularity. (×300)

proved the malignancy of the tumor, originally assumed to be benign, on the basis of the sections then taken.

The great majority of the adenomata with blood vessel invasion are of the embryonal or fetal type. This type of invasion occurring in the simple, the colloid, and the Hürthle cell adenoma is practically unknown.

In any discussion of the adenomata with blood vessel invasion, it is important to point out that this is not the only form of malignancy which may develop in an adenoma. In fact, almost any type of thyroid malignancy may appear on the basis of a preexisting adenoma, and, as has been known for years, 80 to 90 per cent of all thyroid tumors arise from preexisting adenomata. Therefore, there is sound pathologic and clinical evidence for the prophylactic removal of any isolated nodule of the thyroid gland which either is or simulates an adenoma.

The malignant forms of papilliferous tumors of the thyroid and those of aberrant thyroid origin[6] may be discussed together. There is but little essential difference in the behavior of the two groups. In reviewing the

older thyroid literature, it becomes obvious that regions of secondary hyperplasia with papillary projections in nodular goiters, as well as other changes, have been mistaken for true papilliferous tumors of thyroid origin.

First recognized by Wolfler,[25] who described both solid and cystic forms of papilliferous tumors, there was much confusion in the group until differentiated by Graham.[14] The peculiar clinical behavior of these tumors with their marked tendency to repeated local recurrences and failure to metastasize distantly was brought out clearly by Low.[17] Wegelin,[23] in his excellent discussion of the thyroid gland in Henke-Lubarsch, recognizes the existence of the solid and cystic form and recognizes also that papillary proliferations of the nonneoplastic type may occur in other enlargements of the thyroid.

Graham classified the malignant papilliferous tumors into the papilliferous

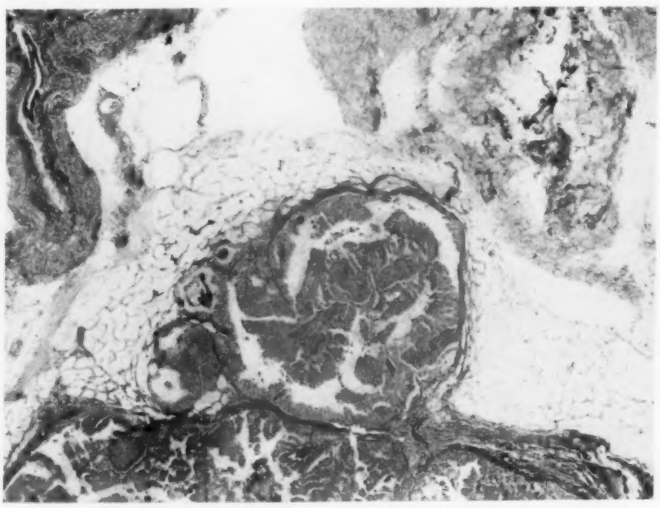


FIG. 7.—Papillary cystadenoma illustrating marked papillary formation and tendency to develop cysts. Note invasion of the perithyroid tissue. (×50)

cystadenocarcinoma of local malignancy, the malignant adenoma with papilliferous differentiation, in which distant metastasis may occur, and a form of papilliferous adenocarcinoma arising independently from any preexisting adenoma.

The classification of the papilliferous tumors has been further clarified by Moritz and Bayless[19] who distinguished five forms of papilliferous tumors: (1) The papilliferous cystadenoma, a benign tumor which represents hyperplasia of the lining epithelium of a cystic adenoma; (2) the papilliferous adenoma, which represents epithelial proliferation of an hyperplastic type within the follicles of a preexisting adenoma, and is nonmalignant; (3) the papilliferous carcinoid, which is differentiated by these authors, probably mistakenly called "papilliferous cystadenomata" by earlier writers, which represents focal papillary hyperplasia, nonencapsulated in a nonneoplastic thyroid

gland; (4) the papilliferous adenocarcinoma arising from malignant change in a papilliferous cystadenoma, which shows capsular invasion or metastasis to regional lymph nodes; and (5) the papilliferous malignant adenoma, which shows a papillary intra-acinar hyperplasia in an adenoma with malignant characteristics, *i.e.*, blood vessel invasion, capsular invasion, and sometimes metastasis to regional lymph nodes.

We include in the present paper only the last two types, and we place the last type—the papilliferous malignant adenoma—in the same clinical group with the malignant adenomata with blood vessel invasion, rather than with the true malignant papilliferous adenocarcinomata. Because of this difference in clinical behavior from the true adenocarcinomata showing some tendency to papillary formation, we have preferred to utilize for this group the term papillary cystadenoma, malignant (Fig. 7). Sometimes there is no extension beyond the primary tumor which shows gross or microscopic evidence of malignancy when explored, but at other times the malignancy is apparent because of either lymph node metastases or because of extensive proliferation with tracheal constriction.

The adenocarcinomata of the thyroid we regard as of moderate malignancy and place in our clinical Group II. These adenocarcinomata almost invariably arise from preexisting adenomata. They differ from adenomata in that they develop a less differentiated type of growth, with greater variation of cell size and shape, much greater mitotic activity, and a marked degree of invasiveness of surrounding tissue. Usually, the development of the adenocarcinoma has destroyed all trace of the preexisting adenoma, and this original nidus can be recognized only from the history given by the patient.

We divide the adenocarcinomata into three histologic groups:

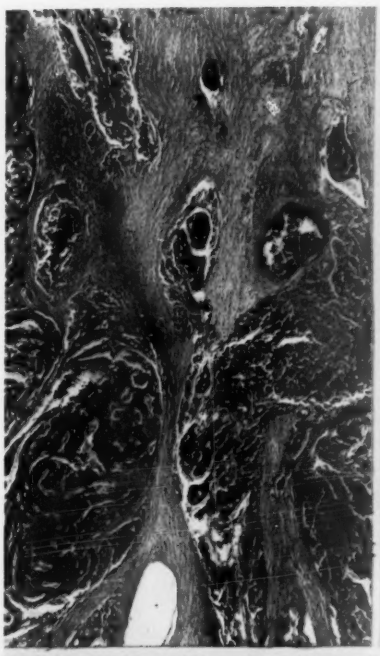
First, the papillary adenocarcinoma. This differs from the papillary cystadenoma by its greater anaplasia and by its lack of encapsulation. The papillary adenocarcinoma freely invades both the thyroid and adjacent normal tissue (Fig. 8). The epithelium is variable in size and shape, but generally polyhedral or cuboidal, with fairly well-defined cell boundaries. The papillary projections are not covered with a single layer of epithelium as in the case of the papillary cystadenoma, but rather the epithelium is heaped up several cells in thickness; here and there masses of cells occur without any lumina whatever; mitotic figures are moderately frequent, and some variation in cell size is prominent. However, definite lumina formed by the tumor may show the formation of colloid.

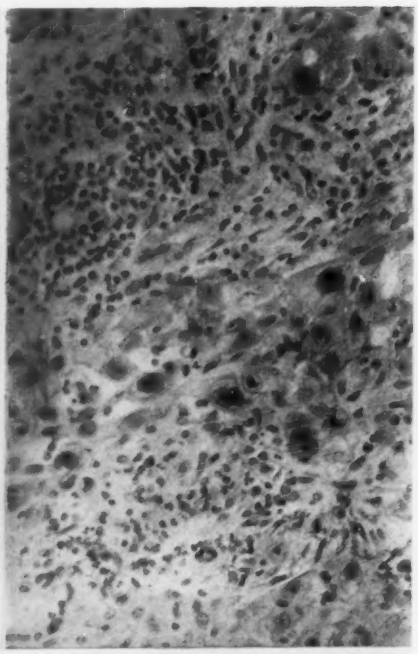
The second type of adenocarcinoma shows no papillary projections and is made up of masses and strands of epithelial cells, usually cuboidal to polyhedral, arranged in a stroma which may be either scant or fairly abundant. Here and there in the clusters definite acini form and these rarely contain colloid (Fig. 9). Not infrequently the mitotic figures may be definitely abnormal, with multiple spindles and marked variation in chromosomal number.

The third type of adenocarcinoma is the rarest, the Hürthle cell adeno-

FIG. 8.

FIG. 9.





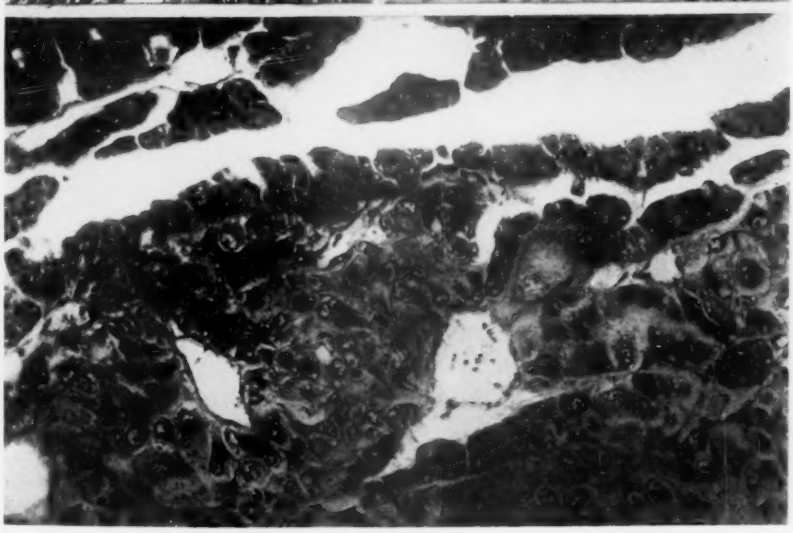


FIG. 10.

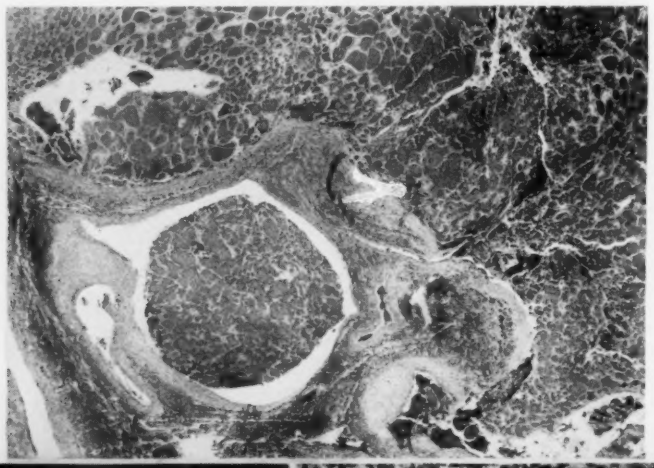
FIG. 8.—Papillary adenocarcinoma showing destruction of the thyroid and invasion of adjacent tissue. (×48)

FIG. 9.—Adenocarcinoma showing polyhedral cells and slight tendency to alveolar arrangement. (×300)

FIG. 10.—Hürthle cell adenocarcinoma, with large, clear, acidophilic cells. (×300)

carcinoma. Here, the same large, clear, acidophilic cells predominate as are seen in the Hürthle cell adenoma, but their arrangement is irregular, small

FIG. 11.



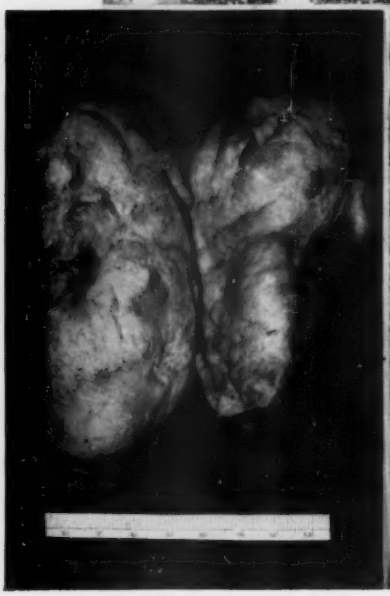


FIG. 12. FIG. 13.

FIG. 11.—Carcinoma simplex of compact type. Note the blood vessel invasion. (×48)
FIG. 12.—Carcinoma simplex of the diffuse type showing resemblance to Hashimoto struma.
FIG. 13.—Carcinoma simplex of the diffuse type demonstrating epithelial cells and irregular arrangement. (×750)

and large masses alternating with varying degrees of lumen formation (Fig. 10). Usually colloid is not present. There is definite invasion of adjacent thyroid tissue and surrounding structures. Mitoses are moderate in number, usually only one or two per high power field. We believe this to be a true thyroid tumor, and not of parathyroid origin, as has been suggested.

The highly malignant carcinomata of Group III represent a heterogeneous group from the histologic standpoint.

The small cell carcinomata, or carcinoma simplex, occur in two forms in the thyroid: The first is the compact type, in which there are solid masses, strands and cords of rather small, cuboidal to polyhedral, deeply staining cells with hyperchromatic nuclei, with a sharply defined distinction between the tumor cells and their stroma (Fig. 11). The mitotic figures are fairly frequent, ranging from one to five per high power field. Invasion of surrounding structures is marked.

In the diffuse form of carcinoma simplex of small cell type, we have a much more complicated picture. Here, at first glance, the tissue might be taken for chronic thyroiditis, particularly the Hashimoto type; at other times, the resemblance to lymphoma is marked (Fig. 12). However, on careful examination, one sees that the cells of the tumor are made up of small, rather irregular epithelial cells with a very small amount of cytoplasm and a rather small hyperchromatic nucleus (Fig. 13). Mitoses are rather infrequent. The tumor cells are scattered irregularly and diffusely through a rather dense, fibrous stroma, which has replaced much of the normal thyroid structure and extended out into the adjacent normal tissue. There are scattered lymphocytes and mononuclear leukocytes infiltrating the stroma as well. The clue to the true nature of the tumor is usually pointed out by small clusters of closely adjacent epithelial cells occasionally taking a pseudo-acinar form.

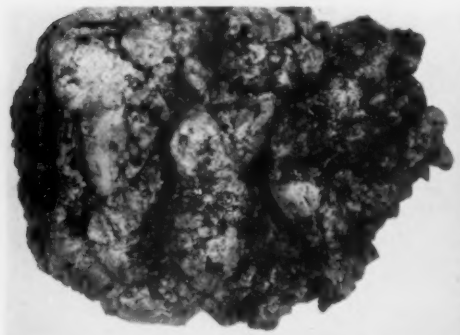
The giant cell carcinoma,[22] sometimes called carcinosarcoma or even fibrosarcoma, has a very characteristic microscopic picture and a characteristic history. These tumors usually occur in females over 50 years of age, and show rapid growth arising from a previous long-standing adenoma. Grossly, they are fleshy, homogeneous, and widely infiltrating (Fig. 14). Their appearance microscopically is bizarre in the extreme (Fig. 15). All types of irregular tumor giant cells with huge, lobulated, often vacuolated nuclei, multiple nuclei, irregular mitoses are mixed indiscriminately with smaller clusters of fairly well-defined epithelial cells and some stromal fibroblasts. Few tumors have a more startling microscopic appearance than do these.

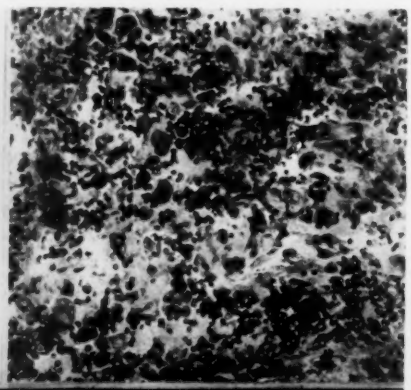
Epidermoid carcinoma of the thyroid is one of the rarest tumors. This has two possible sources of origin: thyroglossal duct remnants on the one hand, and metaplasia of thyroid epithelium on the other.[16] In the instances we have seen, it has been practically impossible to tell from which source these tumors arose.

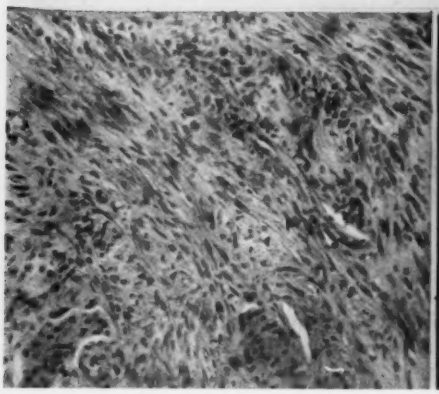
True fibrosarcoma may arise from the stroma of the thyroid gland, although it is extraordinarily rare.[26] The great majority of the cases of fibrosarcoma or of carcinosarcoma are the gaint cell carcinomata which we do not regard as being of mesenchymal nature. The only criterion on which we are willing to accept the fibrosarcoma of the thyroid is that of a typical sarcoma arising within the substance of the thyroid, the cells of which show definite collagen or fibroglial fibrils (Fig. 16).

True lymphoma of the thyroid may occur (Fig. 17) and this must be distinguished from the carcinoma simplex of diffuse type. It must also be distinguished from the struma lymphomatosum of Hashimoto. The criteria for lymphoma here are the same as those elsewhere. Almost always, however, thyroid involvement is secondary to tumor elsewhere. The occurrence of definitely abnormal lymphoblastic cells arranged without regard to the anatomic conformation of the tissue infiltrated on the one hand and without

FIG. 14. FIG. 15.







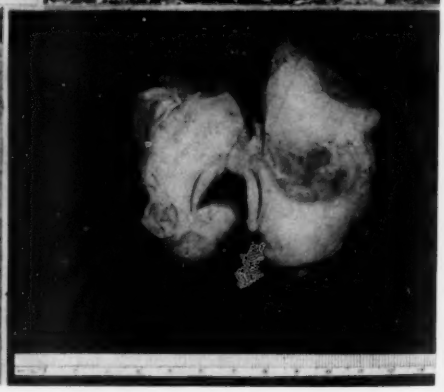


FIG. 16. FIG. 17.

FIG. 14.—Giant cell carcinoma, showing fleshy appearance and infiltrating character.
FIG. 15.—Giant cell carcinoma; note the large, bizarre giant cells and irregularity of arrangement. (×300)
FIG. 16.—Fibrosarcoma showing typical fibroblastic cells with abundant formation of collagen. (×250)
FIG. 17.—Lymphoma of the thyroid. Cross-section of the thyroid and trachea showing diffuse infiltration of tissues by lymphoma cells.

regard to the formation of typical lymph nodular structures on the other hand is characteristic. While infiltration may be extensive in the struma lymphomatosum of Hashimoto, there is practically always clear-cut secondary follicle formation. The lymphocytes are normal in appearance and they infiltrate between the acini in orderly manner.

We have also seen Hodgkin's disease of the thyroid, which has exactly the same appearance and behavior as it has elsewhere.

Radiation Treatment.—The first report of the value of radiation therapy was by Pfahler,[21] of Philadelphia, who reported a case in which operation was performed three times for carcinoma of the thyroid. The patient lived two years after beginning treatment and died of metastasis to the cervical spine. There was no evidence of local disease at the time of death. Pfahler reported another patient living and well three years following radiation therapy after partial excision and confirmation by histologic study.

In 1922, James Case[5] reported a case of thyroid malignancy in which histologic evidence of malignancy was made at operation in 1914. Radiation treatment was started soon after surgical procedure and in 1922, eight years later, the patient was alive and well without evidence of recurrence.

Haagensen[15] was the first to report the value of radiation therapy and to correlate it with the various histologic types, using the histologic classification suggested by Ewing.

Various studies have been made upon the frequency of malignancy in clinically nodular goiters. The incidence of malignancy, as reported by Balfour[1] in 1918, was 1.6 per cent in 6,359 cases of nonexophthalmic goiter at the Mayo Clinic. In J. H. Means'[18] monograph on the thyroid, he mentioned that carcinoma was proved to be present in 3.2 per cent of clinically nodular goiters.

In 1937, Murphy and Ahnquist[20] demonstrated that proliferation may take place in multiple colloid adenomatous goiters forming nodules and classed as fetal adenomata.

Radiation treatment of carcinoma of the thyroid has been employed since 1914, and varying reports in the literature give evidence of its value, although there are several instances of moderately large series of cases in which radiation therapy has been employed and no beneficial effects were obtained. It is to be noted that during the first years of treatment radiation was given merely as a palliative measure to control the disease symptomatically for as long as possible. During this time the pathologic classification was satisfactorily developed, as was the surgical treatment, and to-day we are in a position to judge the pathologic type of thyroid cancer which will respond to radiation therapy. It is not only with a palliative intent that we now start treatment but with the desire to bring about five- and even ten-year cures of this disease which heretofore has been practically impossible in the more severe types of thyroid malignancy.

It will be noted from the pathologic classification given in this paper that thyroid tumors must be divided into two types, namely, benign and malignant. We are not interested in the benign type since such tumors are handled satisfactorily surgically, and no radiation treatment is indicated. Radiation therapy for the benign types of thyroid tumor is contraindicated. It is on the malignant group that radiologists must center their attention and realize

there are several degrees of malignancy with which they must deal. We know that the tumors falling into Group I are of low or potential malignancy, and in many of the cases temporary if not permanent cure can be obtained by surgery alone. It has been our experience, however, in the advanced cases, in which radical operation cannot be performed, that many of these tumors decrease in size and some disappear following moderate amounts of radiation treatment, and in those cases in which recurrence took place after operation radiation therapy was of distinct value in controlling the disease over a period of years. It seems necessary to us in each case of thyroid cancer to give radiation therapy, even though the tumor is of low and potential malignancy. We believe the results reported in this paper will bear out the necessity of radiation treatment to obtain a high percentage of cures.

In the tumors of Group II and Group III, which are of moderate and high malignancy respectively, only a few will respond favorably to operation alone and we now know that most of the good results with radiation come when as much of the tumor has been removed surgically as possible. The end-results depend upon radiation therapy being given in large, protracted doses to destroy the tumor completely. Our experience with some types of tumor in the high malignancy group has been small, namely, the giant cell carcinoma and the epidermoid carcinoma. It has been impossible to determine the lethal tumor dose of radiation necessary to destroy these tumors, but in no case has a satisfactory result been obtained even when radiation was used as a palliative procedure. We believe from the few cases of this type which we have seen that it will be impossible to destroy giant cell or epidermoid carcinoma without destroying normal surrounding tissue.

In the moderately malignant group, namely, the papillary adenocarcinomata, the alveolar adenocarcinomata, and the Hürthle cell carcinomata, it is of interest to note that prior to 1932 operation plus radiation treatment was of practically no value except in isolated cases. The results in this group of cases show that the improvement is now brought about by the larger doses of roentgen rays given postoperatively.

We start radiation treatment as soon after the surgical operation as the condition of the patient warrants, which is usually within one week. There need be no fear of the wound failing to heal by giving radiation therapy after five days. A large percentage of the patients here reported have been treated by a routine method in order to determine the lethal tumor dose of the various types of malignant cells. We have learned the amount of radiation necessary to destroy those tumors which can be successfully treated by radiation.

A cross-fire method of radiation has been found to be preferable in this type of lesion. One treatment is given daily to each of three portals, using one portal on each side of the neck and one in the midline, being careful not to overlap the fields but centering the rays so that the largest percentage of the radiation will enter the tumor bed. The size of the portal depends on the size of the original growth and the degree of substernal extension which the tumor has attained. We have usually been able to use a 7 cm. square

portal on each side of the neck and in the midline without overlapping the field, and in this way have covered the entire tumor bed. A total of 2,000 r units is given to each portal, to make a total dose of 6,000 r units delivered to the skin during one series of treatments. Each portal is treated daily after the first three treatments, giving 150 r units to each, making a total of 450 r units daily. If the patient is debilitated it is necessary to decrease the dose to 100 r units to each portal daily. A total of 6,000 r units given externally on the surface gives a dose of approximately 4,800 r units 2 cm. beneath the skin area, which we believe is fair to assume as the total depth dosage, although no direct measurements have been made in our cases. The following factors have been used:

K.V.P. 200, milliamperes 20, r units per minute 24.
Filter 1 Mm. copper, 1 Mm. of aluminum added.
Distance 50 cm., portal 7 sq. cm., half value layer 0.11.
Treatments are carried on daily except Sunday unless complications arise.

Complications of Radiation Treatment.—The most common complication of radiation treatment is radiation sickness which is quite common when large amounts are administered. Radiation sickness may come on immediately following the treatment or two to six hours later. The symptoms are nausea and vomiting, associated with a generalized feeling of unrest and irritability. We have tried numerous medications to control radiation sickness but for the most part none of them has been successful, although in a few cases striking results have been obtained by the use of vitamin B_1 in large doses. This is not a serious complication as it usually clears within 72 hours after radiation has been completed.

The most important complication following radiation treatment is radiation dermatitis which may in some cases be quite severe and require six to eight weeks to heal entirely. Radiation dermatitis will occur with this dosage in approximately seven to ten days following treatment. Laryngitis and tracheitis as well may develop but disappear in nine to ten weeks' time.

We have had no fatal results from radiation treatment alone, but several of our patients have had to be hospitalized owing to difficulty in swallowing following treatment.

Results.—In tabulating the results of this series of cases it was necessary to review the entire group of cases of thyroid cancers which have been studied in the clinic from a clinical and pathologic angle in order to reclassify these tumors properly. In so doing, all questionable cases of malignancy were discarded and the tabulation of our results varies from that previously reported. We believe by so studying these cases we have been able to correlate successfully the clinical, pathologic and radiologic pictures of this disease.

SUMMARY

The relationship of malignancy to preexisting adenomata of the thyroid gland is discussed.

Illustrative cases demonstrating the penalty of delay in the removal of discrete adenomata are presented.

The clinical diagnosis of malignancy of the thyroid is discussed, together with the diagnosis, management, and dangers of malignant degeneration in lateral aberrant thyroid.

The surgical approach to malignancy of the thyroid gland combined with roentgenotherapy is discussed and the method of radically removing one or both lobes of the thyroid, with the sternomastoid muscle and internal jugular vein is discussed and illustrated.

Mention is made of the contraindications for undertaking operation and the contraindications for continuing operation after it has once been undertaken.

The pathology of thyroid malignancy, together with a grouping, is presented.

The radiation treatment of thyroid malignancy and the five-year survival rates following combined radiation and surgical treatment are presented.

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STUDIES RELATING TO THE PATHOGENESIS OF CHOLECYSTITIS, CHOLELITHIASIS AND ACUTE PANCREATITIS *

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Until comparatively recently the pathogenesis of both cholecystitis and cholelithiasis was ascribed solely to infection. Since, however, there were several clinical and pathologic features about the disease which were inconsistent with this hypothesis, investigation was stimulated. From the studies there have accumulated many excellent clinical and experimental data which not only minimize further the importance of infection but establish, rather definitely, certain other pathogenic factors.

There has accumulated a preponderance of evidence to indicate that biliary stasis is a very constant and, therefore, basic factor, but there is also good evidence that stagnation of bile does not in itself cause permanent pathologic changes in the gallbladder. Such changes are, in all likelihood, dependent upon other agents which either accompany stasis or result indirectly from it.

It has been demonstrated repeatedly that the wall of the gallbladder becomes edematous or inflamed from several factors, among which may be mentioned abnormal changes in the chemistry of the bile, particularly as these relate to alterations in its hydrogen ion concentration, the presence of pancreatic enzymes in the bile, and overdistention of the viscus. It has also been demonstrated repeatedly that when the gallbladder wall is edematous or inflamed its selectivity in its absorptive and secretory capacity becomes altered. Likewise, the damaged wall becomes more vulnerable to infection. Thus, an abnormality in the constituency of bile due to stasis, hepatic damage, the presence of pancreatic ferments or other factors, may cause pathologic changes in the wall of the gallbladder and, in turn, these changes alter further the chemistry of the contained bile and upset the balance by which certain of its constituents are held in solution. This results in their precipitation and the formation of stones. For example, it has been shown that when the bile salt-cholesterol ratio falls below a critical level, cholesterol crystals appear in the bile.

Detailed accounts of these facts and other related clinical and experimental observations are recorded in the reports of the excellent studies of Rous, McMaster and Drury; Ivy and Walsh; Mann, Foster and Brimhall; Andrews, Schoenheimer, Hrdina, Dostal and Aronsohn; Elman and Graham; Phemister, Aronsohn, Pepinsky, Day and Hastings; Ravdin, Johnston, Austin, Riegel and Rose; Dolkart, Jones, and Brown; Doubilet and Colp; Cooper and Illingworth; Whitaker; Feldman, Morrison, Krantz and Carr; Walters, Greene and Fredrickson; and Wolfer.

* Read before the American Surgical Association, St. Louis, May 1, 2, 3, 1940.

In an excellent piece of work, Wolfer has presented evidence which suggests that, under certain circumstances, pancreatic juice in man could and unquestionably does pass by reflux into the gallbladder. He, among others, quoted by him, has shown that the instillation of unfiltered pancreatic juice into the gallbladder of animals is followed by pathologic changes which vary from edema to complete necrosis of the wall. The same results were produced by instillations into the common duct. This subject of pancreatic reflux has

FIG. 1.—Postoperative cholangiogram. Iodized oil injected through a catheter in the common duct filled not only the much dilated biliary ducts but also the duct of Wirsung. There is a filling defect at the ampulla of Vater, presumably from a stone impacted in it. None of the radiopaque solution entered the duodenum. The common passageway between the common duct and the duct of Wirsung is well demonstrated in addition to the obstruction and stasis and dilatation of the ducts resulting from it. (Courtesy of Dr. R. R. Best.)

been discussed at length by Wolfer so only a few salient facts will be presented here. It is a pertinent fact that the pancreatic duct joins the common duct or shares with it a common opening at the ampulla of Vater in a large percentage of people. Mann and Giordano found this relationship in 45 per cent of the specimens which they studied, while Cameron and Noble, Westphal, and Elman found it to exist in 65, 84 and 59 per cent, respectively. With an obstruction at the ampulla, as shown in Figure 1, this continuous passageway between the ducts permits pancreatic secretions to mix with the

bile in the common duct and with it pass into the gallbladder. Reflux of this sort unquestionably takes place in the presence of obstruction and therefore in conjunction with stasis. It is possible that it occurs in the absence of obstruction and stasis. That pancreatic secretions do enter the gallbladder in man has been shown repeatedly by demonstrating the presence of pancreatic enzymes in the gallbladder bile in cases with acute cholecystitis.

Our interest in the subject of pancreatic reflux was aroused by observations made upon a patient who died from total loss of bile and pancreatic secretions through a cholecystocutaneous sinus.

Case Report.—A male, age 38, had, when seen by his surgeon, a typical clinical picture of acute cholecystitis of 12 hours' duration. There had been two previous similar attacks of pain within the past three months. A mild degree of jaundice which had followed the second episode had persisted up to the onset of the present one.

He was operated upon immediately, and a moderately distended, thick-walled, markedly edematous and inflamed gallbladder was found amid a few fibrinous adhesions and a small amount of bile stained fluid. The gallbladder contained no stones. A cholecystostomy was performed.

Immediately following operation and continuing until his death, 12 days later, there was a very copious and almost continuous drainage of clear or slightly bile tinged fluid. It drained through the tube for 48 hours and thereafter from the wound.

He was seen in consultation by one of us (J. D. B.) on the sixth day after operation. The wound in the abdominal wall was wide open and its surfaces fiery red. Copious quantities of clear fluid welled up in the wound almost constantly. The skin of the abdominal wall for a wide area about the wound was fiery red and showed considerable digestion.

The patient was extremely dehydrated despite the parenteral administration of two to four liters of fluids daily. The eyes and cheeks were sunken, the pulse thin, its rate 120 to 140, the blood pressure 80/40, the rectal temperature 96.2° to 98° F., and there was extreme asthenia. Blood chlorides were 210, sodium 205, and postassium 25.

With restoration of a more nearly normal fluid and mineral balance by increasing intake, the temperature, pulse, blood pressure, and urinary output assumed fairly normal levels and the general appearance improved remarkably for a few days.

From a first impression, a diagnosis of duodenal fistula (probably originating from a surgical accident) was entertained. However, aniline dyes and charcoal, given by mouth, did not appear in the fluid draining from the wound and could not be demonstrated in it. But the dyes subsequently appeared in the stools. Lipiodol, injected through a catheter which had been passed for some distance into the sinus tract, filled the extrahepatic ducts down to the ampulla where a small quantity entered the pancreatic duct. None entered the duodenum.

The drainage fluid contained both amylase and trypsin in the two samples examined. A postmortem examination could not be obtained. However, from the evidence, there can be little doubt that there existed a complete obstruction at the ampulla, and, as a result pancreatic secretions passed up the common and cystic ducts and through the gallbladder to be discharged through the sinus.

We have subsequently operated upon two cases with acute nonperforated gangrenous cholecystitis with regional bile peritonitis. Cultures from the abdominal fluid, from the bile, and from the wall of the gallbladder in both cases were sterile. But the gallbladder bile in both cases contained both amylase and trypsin. The peritoneal fluid was not examined for enzymes. Colp, Gerber, and Doubilet have reported three similar cases. Two had bile

peritonitis and sterile gallbladder bile. In one, the bile contained *B. coli* and *B. Freidländer*. In all of them, the gallbladder bile contained pancreatic enzymes.

Many of the current opinions regarding the pathogenesis of gallbladder disease are based upon observations made upon laboratory animals which seldom, if ever, develop the disease. There are, however, certain domestic animals—cattle, sheep and goats—which frequently develop gallbladder disease. Yet the problem as it exists in these animals has received little or no attention. Nor have these animals been utilized for purposes of investigating the problems of gallbladder disease. With these thoughts in mind, several visits were made to a local packing house, and some interesting facts were

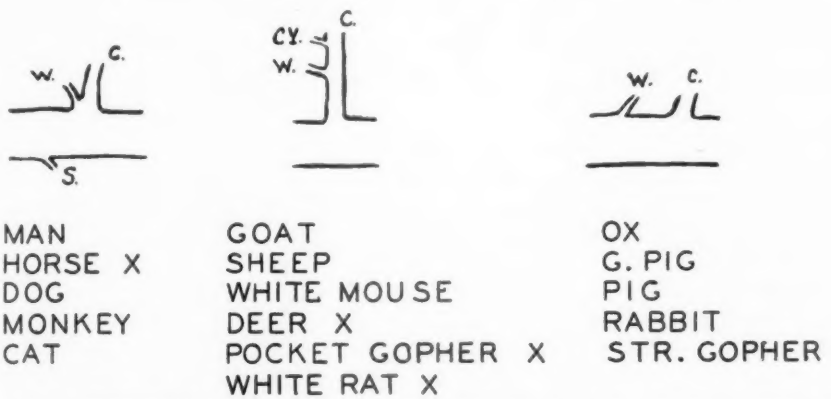


FIG. 2.—Diagrammatic illustration of the anatomic arrangement of the common, hepatic, and pancreatic ducts in man, and in the common laboratory and domestic animals (taken from Mann, Foster and Brimhall). (X.) Animals which have no gallbladder. Ducts: (C.) Common hepatic; (CY.) Cystic; (W.) Wirsung; (S.) Santorini.

obtained: Gallbladder disease occurs infrequently in swine, commonly in sheep and goats, and less commonly in cattle. It occurs principally in the form of stones, and almost entirely in the older animals. The stones, with few exceptions, are of one type, *i.e.*, bile pigment. In most instances, the gallbladder containing the stones is normal in gross appearance.

In sheep, however, chronic cholecystitis, with or without stones, occurs not infrequently, and curiously enough the liver and bile ducts of animals in which there is cholecystitis usually show evidence of active or past infestation with liver flukes. Since these parasites are large, it would appear that they might readily produce a temporary obstruction of the common bile duct as they ascend it. This possibility should be borne in mind in connection with the anatomic arrangement of the ducts as shown in Figure 2, and the experimental observations which follow.

EXPERIMENTAL STUDIES

As stated above, all previous investigations of gallbladder disease have been carried out in animals which, under normal circumstances rarely, if ever, develop the disease. Furthermore, the experimental procedures which

have been employed to study various phases of the problem have had to introduce, as a matter of necessity, certain unphysiologic and undesirable factors.

Goats were used in our experiments because the reaction of their gallbladder bile differs little from that of human; because they normally develop gallstones and cholecystitis with a fair degree of frequency; and because the anatomic arrangement of their duct system is remarkably well adapted to the purposes of this study.

In a search for information regarding comparative mammalian anatomy of the hepatic duct system, the report of the observations of Mann, Foster and Brimhall was found. These observations are illustrated in Figure 2. It

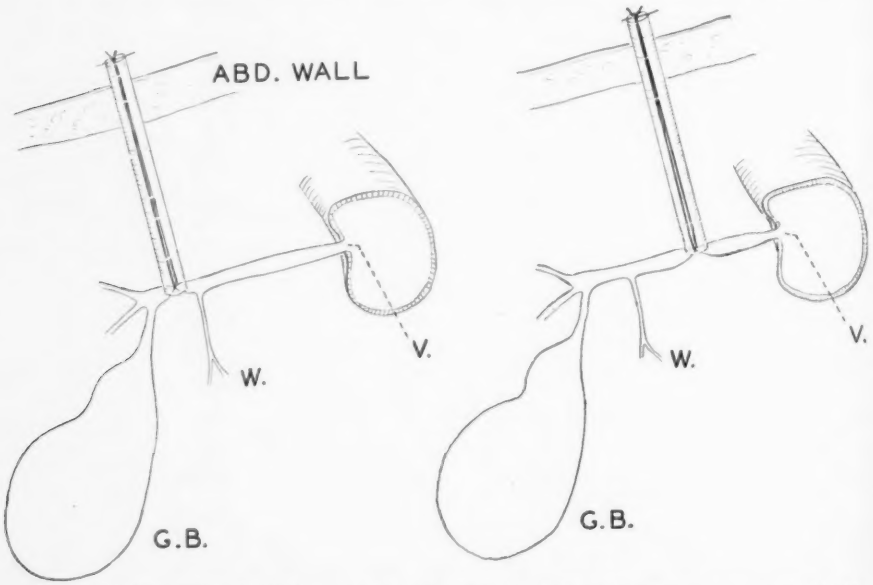


FIG. 3.—Diagrammatic illustration showing the method of inducing temporary obstruction of the common duct. The duct was encircled with a loop of dermal suture, which was threaded through a glass tube with the ends of the loop tied over a button which capped the exteriorized end of the tube. The obstructions were released by cutting the exposed ends of the loop and removing it with the tube. Obstructions above the duct of Wirsung (W.) induced stasis only; below it, stasis plus the reflux of pancreatic secretions. (V.) Ampulla of Vater. (G.B.) Gallbladder.

will be observed that in both goats and sheep the pancreatic duct empties into the common bile duct at a considerable distance proximal to the juncture of the common duct with the duodenum and several millimeters distal to the juncture of the common and cystic ducts. Thus, normally, pancreatic juice mixes with bile in the proximal end of the common duct. It occurred to us that, in the event of an obstruction at the distal end of the common duct, not only would stasis be produced but also an opportunity would be afforded for the reflux of pancreatic secretions into the gallbladder and of bile into the pancreas. On the other hand, an obstruction of the common duct immediately proximal to the pancreatic duct and yet distal to the cystic duct would result in biliary stasis alone. If we assume that stasis and reflux in man are brought about by an obstruction at the ampulla of Vater, then we have, in man, a

situation closely simulating that produced in our experiments, by the simple expedient of temporarily or permanently occluding the ducts. By obstructing the common duct at the two levels (above and below the pancreatic duct) an opportunity was afforded for a comparison of the effect upon the gallbladder of stasis alone with that of stasis plus the reflux of pancreatic secretions.

The common duct was obstructed by two methods. In one group of goats, the obstructions were made permanent with ligatures of silk. In the other group, temporary obstructions were created by means of plain catgut ligatures in two goats and by a special method in the remaining ones. This method consisted of passing a loop of dermal suture material around the common duct. The ends of the loop were threaded through a glass tube and tied over a button which capped the outer end of the tube. This tube was long enough to extend from the common duct out of the abdomen and beyond the surface of the skin. Obstructions were maintained for periods varying from 24 hours to six days. They were released by cutting the exteriorized ends of the loop and removing it with the tube (Fig. 3).

PROTOCOLS OF EXPERIMENTS

Classified Report of Individual Animals

GROUP 1.—*Permanent Obstruction Distal to Juncture of Pancreatic Duct*

Goat No. 4.—Approx. age, one month. *Diagnosis:* Acute, nonperforated gangrenous cholecystitis, with bile peritonitis and acute pancreatitis with local fat necroses.

The common duct was obstructed by permanent ligature distal to the entrance of the pancreatic duct. The animal was killed when moribund, three days later.

Gross Pathology.—Tissues of the abdominal wall and peritoneal cavity were bile stained. The abdomen contained several ounces of bile stained fluid, but there were no adhesions. The gallbladder was enormously distended but intact, and its surface was dull and deeply stained. It contained thick dark brown fluid, turbid with chunks of reddish-brown and black friable material. The fluids from the peritoneal cavity and gallbladder were sterile on culture, and both contained amylase (activity of 20 and 100, respectively). The gallbladder fluid also contained trypsin (activity of 1.2) and occult blood. The extrahepatic ducts were moderately dilated above the ligature. The pancreas was enlarged, tense, and studded with reddish-brown areas, and the surrounding tissues showed fat necrosis. Proximal to the ligature, all extrahepatic ducts were greatly dilated. The liver was pale, enlarged and its edges rounded. The regional lymph nodes were enlarged.

Microscopic Findings.—Gallbladder: The epithelium was gone except for minute, scattered remnants in the depths, and there was edema of all layers but principally of the serosa, and all tissues were partially necrotic. There was no cellular infiltration. Pancreas: The ducts were dilated and many contained bile. Throughout there were areas of fat necrosis and digestion of the acinar tissue. Liver: There was much bile pigment and some congestion. Kidneys: Normal.

Goat No. 5.—Approx. age, one month. *Diagnosis:* Acute cholecystitis, early acute pancreatitis and early multiple liver abscesses. Pneumonia.

The common duct was obstructed by permanent ligature distal to the entrance of the pancreatic duct. Death occurred 22 hours later. There was bronchopneumonia of both lungs.

Gross Pathology.—The gallbladder was free from adhesions and moderately distended, and the extrahepatic ducts were moderately dilated above the ligature. The gallbladder fluid was thick, brown, and contained reddish-brown soft masses. Cultures of the fluid were negative. Pancreas was enlarged and tense, and on its surface were scattered red areas. The liver was enlarged and slightly mottled. There was regional lymphadenopathy.

Microscopic Findings.—Gallbladder: The surface was devoid of epithelium except in the depths of the folds. There was moderate edema of the wall, mainly of the serosa, and some pigment in the submucosa, but nowhere any cellular infiltration. Common duct: Changes were essentially the same as those of the gallbladder except that the tissues were partially necrotic. Pancreas: Scattered areas of digestion and necrosis but no infiltration of leukocytes. Liver: A few areas of necrosis with and without collections of polymorphonuclear cells. Kidneys: Normal.

Goat No. 7.—Approx. age, one month. *Diagnosis:* Acute nonperforated gangrenous cholecystitis with bile peritonitis; early acute pancreatitis and multiple early liver abscesses.

The common duct was ligated distal to the entrance of the pancreatic duct. Death occurred 20 hours later.

Gross Pathology.—The upper part of the abdomen contained a few ounces of a bile stained fibroseropurulent exudate. The gallbladder and ducts were moderately distended but intact. The gallbladder fluid was thin and turbid with bits of soft dark brown and reddish-brown material. It contained occult blood and both trypsin (activity of 2.2) and amylase (activity of 80). Culture from the gallbladder wall and from the fluid were *B. coli* and gram-negative cocci. The pancreas was enlarged, tense, firm, and mottled with reddish-brown areas. The liver was enlarged and mottled.

Microscopic Findings.—Gallbladder: Devoid of epithelium and the wall infiltrated extensively with lymphocytes and polymorphonuclear leukocytes. All tissues were undergoing necrosis. Common duct: Same changes as found in the gallbladder. Pancreas: Marked dilatation of both ducts and acini. There was necrosis of both fat and acinar tissue and infiltration with both lymphocytes and polymorphonuclear leukocytes. Liver: There were scattered areas of necrosis of liver cells with collections of both mononuclear and polymorphonuclear leukocytes.

Goat No. 8.—Approx. age, one month. *Diagnosis:* Acute gangrenous nonperforated cholecystitis and acute pancreatitis with local peritonitis. Acute hepatitis with multiple abscesses.

The common duct was permanently ligated distal to the juncture of the pancreatic duct. Autopsy five days later.

Gross Pathology.—The tissues of the abdominal wall and peritoneal cavity were bile stained. There were two or three ounces of bile stained fluid in the right upper quadrant. The gallbladder was buried in a mass of adhesions, and it and the extrahepatic ducts above the ligature were greatly distended. The gallbladder was slightly thicker than normal, dark green in color and had no tissue luster. It contained thin greenish-brown fluid in which there were many particles of soft brown material. The fluid contained both trypsin (activity of 1.2) and amylase (activity of 100); and from the fluid were cultured *B. coli* and gram-positive and -negative cocci. The pancreas was enlarged, tense, and bluish-pink in color. Its duct appeared to contain bile. The liver was very large and mottled and its edges were round. Regional lymph nodes were much enlarged.

Microscopic Findings.—Gallbladder: The epithelium was gone and the other tissues were entirely necrotic. The wall was considerably thickened by edema. Liver: There were small scattered areas in which hepatic cells were undergoing necrosis, also multiple small abscesses characterized by collections of polymorphonuclear leukocytes. There was also an increase in young connective tissue. Pancreas: The pancreatic ducts were dilated and there were scattered areas of necrosis of acinar cells and of fat. All blood vessels were congested. Kidneys: Normal.

Goat No. 13.—Approx. age, one month. *Diagnosis:* Acute cholecystitis.

The common duct was ligated distal to the juncture of the pancreatic duct. Autopsy was performed soon after death, six days postoperatively.

Gross Pathology.—Both the gallbladder and common duct (above ligature) were enormously distended, edematous, moderately thick-walled and adherent to neighboring tissues. Bile could be seen in the dilated pancreatic duct. The pancreas appeared to be definitely larger than normal. The gallbladder bile was greenish-brown with small masses of friable material. It contained both trypsin (activity of 0.8) and amylase (activity of 20); and cultures showed the presence of *B. coli* and gram-negative and -positive cocci.

Microscopic Findings.—Gallbladder: The wall was considerably thickened with edema which was most apparent in the serosa. The vessels were dilated, the wall infiltrated with lymphocytes and a few polymorphonuclear cells, and the mucosa devoid of epithelium except in the depths of the folds. The common duct showed the same changes. Pancreas: Both ducts and acini were widely dilated. There was, however, no necrosis or other change. Liver: Essentially normal except for moderate dilatation of the hepatic ducts. Kidneys: Normal.

Goat No. 1.—Approx. age, 15 months. *Diagnosis:* Acute cholecystitis with gangrene, perforation and localized peritonitis.

The common duct was ligated distal to the juncture of the pancreatic duct. Autopsy was performed 11 days later.

Gross Pathology.—Tissues of the abdominal wall were bile stained. The gallbladder was densely adherent to neighboring tissues. Between the stomach and gallbladder there was a small abscess of two or three ounces of thick fluid containing bile. This abscess communicated with the gallbladder which had perforated through a necrotic area. The gallbladder wall was very thick, translucent,* and the external surface was milky-white with a red overcast from dilated congested blood vessels. The mucosa was intensely inflamed.

The gallbladder contained thick greenish-brown fluid and small pieces of brown friable material. The fluid was strongly positive for occult blood, and from it were cultured *B. coli* and gram-negative cocci. It was not examined for the presence of pancreatic ferments. The distal end of the common duct could not be identified.

Microscopic Findings.—Gallbladder: The wall was very thick, the mucosa necrotic and the epithelium gone. There was profuse infiltration of the submucosa with polymorphonuclear leukocytes, with formation of multiple abscesses. The remainder of the wall was considerably infiltrated with both polymorphonuclear and monunuclear cells. There was also moderate edema and fibroblastic infiltration.

* Upon emptying these gallbladders, however, they lost most of their slate-green color. It seems that the gallbladder wall can be much thickened with edema and yet permit the green color to show through, whereas much less thickening of the wall with fibrous tissue renders them opaque.

Pancreas and kidneys: Normal. Liver: Some fatty degeneration and a few interstitial polymorphonuclear leukocytes.

Goat No. 2.—Approx. age, 14 months. *Diagnosis:* Acute, nonperforated gangrenous cholecystitis with local bile peritonitis.

The common duct was ligated distal to the entrance of the pancreatic duct. Twenty-six hours later, the animal was moribund and, therefore, was killed.

Gross Pathology.—The peritoneal cavity contained about four ounces of bile stained fluid. The peritoneal surfaces were inflamed. The gallbladder was moderately distended and dull in appearance. It contained thin greenish-brown fluid in which there were many small friable brown masses. The fluid was sterile to culture, and contained both trypsin (activity of 2.4) and amylase (activity of 180). The extrahepatic ducts were moderately distended above the ligature.

Microscopic Findings.—Gallbladder: The wall was thin and almost entirely necrotic. There was no cellular infiltration and only slight edema. Pancreas: Essentially normal. Liver and kidneys: Essentially normal.

GROUP II.—*Temporary Obstruction Distal to Juncture of Pancreatic Duct*

In some of the kids listed under permanent obstructions, temporary obstructions were intended but failed because the animals died too soon.

Goat No. 14.—Approx. age four months. *Diagnosis:* Acute, nonperforated cholecystitis and acute pancreatitis with peritonitis.

The common duct was obstructed temporarily with a ligature of plain catgut distal to the juncture of the pancreatic duct. Death occurred 19 days later.

Gross Pathology.—The tissues of the abdominal wall were bile stained. The abdomen contained approximately 800 cc. of bile stained fluid. The peritoneal surfaces were inflamed. The gallbladder was enormously distended and its walls widely adherent to neighboring tissues. The wall was intact, moderately thickened, and its mucous surface smooth with, in many places, hemorrhagic areas. The common duct was widely dilated above area of stenosis and its wall thickened. It was not patent; the ligature had resulted in stenosis. The gallbladder bile was greenish-brown and contained many soft brown particles. It contained both trypsin (activity of 1.5) and amylase (activity of 60) and *B. coli* and gram-negative cocci in both smear and culture. The pancreas was enlarged, firm, and tense.

Microscopic Findings.—Gallbladder: The wall was markedly thickened with edema mainly in the serosa. It was also partially necrotic and contained a few collections of leukocytes. Bacteria were seen in the tissues. Pancreas: Almost entirely necrotic. Bacteria were seen in the tissues. Liver: Essentially normal except for a few small collections of lymphocytes and polymorphonuclear leukocytes.

Goat No. 16.—Approx. age, 14 months. *Diagnosis:* Acute gangrenous cholecystitis with perforation.

The common duct was ligated with plain catgut as a temporary ligature distal to the juncture of the pancreatic duct. The animal began failing 30 days later, and was autopsied 32 days postoperatively.

Gross Pathology.—The gallbladder and common duct were distended and were densely adherent to surrounding tissues which walled off a cavity containing approximately six ounces of bile. This fluid contained brown friable particles. The cavity communicated with a perforation of the gallbladder. The gallbladder bile contained both trypsin (activity of 2.0) and amylase (activity of 80); and cultures yielded *B. coli* and gram-negative cocci.

Both pancreas and liver appeared to be normal. The common duct was almost completely occluded by the inflammatory process around it.

Microscopic Findings.—Gallbladder: The wall was thickened considerably with edema mainly in the serosa. It was partially necrotic and the epithelium was gone except for fragments in the depths of the folds. Liver: Some fatty degeneration, otherwise normal. Pancreas: Essentially normal.

Goat No. 17.—Approx. age, 14 months. *Diagnosis:* Chronic cholecystitis.

The common duct distal to the juncture of the pancreatic duct was obstructed for 48 hours by the temporary occlusive method.

Gross and Microscopic Pathology.—Four weeks later, the gallbladder was explored and found buried in adhesions. Bile was aspirated and found to contain both trypsin (a trace) and amylase (activity of 40), red blood cells 40–50, and leukocytes 1–15 per H.P.F. Cultures were sterile. A biopsy was taken from the wall. It showed a marked inflammatory reaction with edema, much leukocytic infiltration, a loss of epithelium from the mucosa and some fibrosis.

The animal was killed six months later. The gallbladder was normal in size, buried in adhesions, opaque and grayish-white in color, with dilated vessels over its surface. It contained normal bile. The mucosa was red and hyperplastic. From the bile was cultured *B. coli*. The common duct was patent but was enormously dilated above the point of temporary obstruction. The regional lymph nodes were enlarged and there was edema of the gallbladder and neighboring tissues.

Microscopic Findings.—Gallbladder: The wall was thickened with some edema, some fibrosis and extensive lymphocytic infiltration. The mucous surface was devoid of epithelium except in the depths of the folds. Common duct: Changes similar to those of the gallbladder. Pancreas: Normal. Liver: Normal. Kidneys: Normal.

Goat No. 18.—Approx. age, 14 months. *Diagnosis:* Chronic cholecystitis.

The common duct distal to the juncture of the pancreatic duct was obstructed for 48 hours.

Gross and Microscopic Pathology.—Essentially the same as those of Goat No. 17. From the gallbladder bile was cultured *B. coli.*

Goat No. 19.—Approx. age, 14 months. *Diagnosis:* Chronic cholecystitis and cholelithiasis.

The common duct was obstructed distal to the juncture of the pancreatic duct for 96 hours. An exploratory operation was performed one month later.

Gross Pathology.—The gallbladder was buried in adhesions. It was normal in size and the wall was edematous, very thick, opaque, and grayish-white in color. Clear, light green bile was aspirated. It contained both trypsin (activity of 0.5) and amylase (activity of 40). From it were cultured *B. subtilis, B. coli* and gram-negative cocci.

The animal was killed six months after operation. The gallbladder was buried in dense adhesions. It was thick, opaque and grayish-white in color. The common duct was patent but, nevertheless, it was also enormously dilated and its wall thick. Both gallbladder and common duct contained normal bile and, in addition, many minute bile pigment stones. From the bile, *B. coli* was cultured. Regional lymph nodes were large.

Microscopic Findings.—Gallbladder: The wall was much thickened. There was some edema and much fibrosis of all layers, especially of the serosa. The epithelium was hyperplastic and there were many submucosal collections of lymphocytes. Common duct: Changes same as those of the gallbladder. Pancreas: Normal. Liver: A few collections of leukocytes and some fatty degeneration. Kidneys: Normal.

Goat No. 20.—Approx. age, 14 months. *Diagnosis:* Chronic cholecystitis and cholelithiasis.

The experimental procedure was identical and the gross and microscopic findings essentially the same as those of Goat No. 19. Bile aspirated at the exploratory operation, one month after primary operation, contained no trypsin but amylase (activity of 20), and in culture, *B. subtitis, B. coli* and gram-negative and -positive cocci. Smears contained a few pus cells, crystal and débris. Postmortem gallbladder bile contained *B. coli.*

Goat No. 22.—Approx. age, six months. *Diagnosis:* Acute gangrenous cholecystitis.

The common duct distal to the juncture of the pancreatic duct was obstructed for six days. The animal died two days later, and was autopsied immediately.

Gross Pathology.—The gallbladder was adherent to neighboring structures and was moderately distended. The wall was thickened, slightly injected, edematous, green in color and had no luster. Although all extrahepatic ducts were moderately dilated, the common duct was patent. The gallbladder bile was green but contained both trypsin (activity of 2.2) and amylase (activity of 160); and from it was cultured *B. coli.* Regional lymph nodes were large. No definite cause of death was found.

Microscopic Findings.—Gallbladder: The wall was thick, very edematous and almost entirely necrotic except for fibroblasts. The epithelium was gone and there was no cellular infiltration. Sections from the other tissues were lost.

Goat No. 24.—Approx. age, six months. *Diagnosis:* Chronic cholecystitis and cholelithiasis.

The common duct was obstructed for six days distal to the juncture of the pancreatic duct. Autopsy was performed two and one-half months later.

Gross Pathology.—The gallbladder was densely adherent to edematous neighboring structures. It was normal in size, and the wall was milky-green in color, thick and edematous. It contained normal bile and one large and two small bile pigment stones. The bile contained only amylase (activity of 20); cultures of it were sterile. The wall of the gallbladder contained *B. coli.* The extrahepatic ducts were much dilated and their walls were thickened. The common duct was entirely patent.

Microscopic Findings.—Gallbladder: The wall was moderately thick, showing some edema and some fibrosis, and moderate lymphocytic infiltration. The mucous surface was mainly devoid of epithelium. Common duct: This presented the same changes. Liver: Some fatty degeneration. Pancreas and kidneys: Normal.

Group III.—*Temporary Obstruction Proximal to Juncture of the Pancreatic Duct*

Goat No. 25.—Approx. age, three weeks. *Diagnosis: Normal gallbladder.*

The common duct was obstructed between the junctures of the cystic and pancreatic ducts for 24 hours. Death occurred from a respiratory infection five days later.

Gross Pathology.—The abdominal cavity was normal in appearance except for a few adhesions between the gallbladder and neighboring tissues. The gallbladder was normal in appearance except that it was colored an abnormally dark shade of green. The other viscera were normal. The common duct was patent and not dilated but showed a narrow ring of thickening of its wall at the point where it had been occluded temporarily. The gallbladder bile was normal in appearance. Cultures of it and of the wall of the gallbladder were sterile. It contained a trace of amylase but no trypsin.

Microscopic Findings.—Gallbladder: Essentially normal, possibly slight edema of serosa. Liver, pancreas, and kidneys: Normal.

Goat No. 26.—Approx. age, four weeks. *Diagnosis:* Normal gallbladder.

The common duct was obstructed between the junctures of the cystic and pancreatic ducts for 48 hours. The animal was killed 12 days later.

Gross Pathology.—The gallbladder was adherent to the duodenum and other tissues and was slightly distended, as were the cystic and hepatic ducts. There was some regional lymphadenopathy. The common duct was narrowed by a ring of increased thickness of its wall at the site of temporary

occlusion, but it was patent. The other viscera were normal. The gallbladder bile was normal in appearance. Cultures of it gave no growth. It contained amylase (activity of 7).

Microscopic Findings.—Gallbladder: Essentially normal; possibly slight edema of tissues and slight increase in subephithelial lymphocytes. Liver, pancreas, and kidneys: Normal.

Goat No. 27.—Approx. age, one month. *Diagnosis:* Partial biliary obstruction with subacute cholecystitis.

The common duct was obstructed between the junctures of the cystic and pancreatic ducts for six days. The animal was killed 14 days after operation.

Gross Pathology.—The tissues were slightly icteric. The gallbladder, cystic and hepatic ducts were moderately distended, the ducts were tortuous, and their walls somewhat thickened by edema.

The gallbladder was grayish-green in color, and there were many pericholecystic adhesions. The sentinel lymph nodes were very large. The common duct was almost occluded by a band of dense fibrous tissue at the site where temporary obstruction had been applied; it was patent, however. The duct above this level was moderately distended while below it was normal. The pancreas was enlarged and peculiarly soft in texture. The liver was swollen. The gallbladder bile was normal in appearance. From it was cultured the staphylococcus (probably a contaminant) and a diplococcus. It contained amylase (activity of 6.5) and lipase.

Microscopic Findings.—Gallbladder: Moderate edema involving principally the submucosa and marked subepithelial infiltration of lymphocytes, these cells occurring in large collections. Liver: Intrahepatic ducts dilated and small scattered collections of mononuclear and polymorphonuclear leukocytes around ducts. Pancreas: Normal.

Goat No. 28.—Approx. age, one month.

The common duct was obstructed between the junctures of cystic and pancreatic ducts for three days. The animal was killed 12 days later.

Gross Pathology.—With the exception of some pericholecystic adhesions, the gallbladder and other viscera were normal. The common duct was patent, but was slightly narrowed by a band of increased thickness of its wall where temporary occlusion had been applied. The regional lymph nodes were enlarged. The gallbladder bile appeared to be normal. From it were cultured pneumococci. There was insufficient bile for examination for enzymes.

Microscopic Findings.—Gallbladder: Essentially normal, slight subepithelial lymphocytic infiltration. Liver: Essentially normal. Pancreas: Normal.

GROUP IV.—*Permanent Obstruction Proximal to the Juncture of the Pancreatic Duct*

Goat No. 12.—Approx. age, one month. *Diagnosis:* Acute cholecystitis and acute hepatitis with multiple abscesses.

The common duct was ligated, permanently, above the juncture of the pancreatic duct. The animal died nine days later.

Gross Pathology.—The tissues of the abdominal wall and of the viscera near the gallbladder were bile stained. The gallbladder was adherent to surrounding tissues. It was enormously distended and grayish-green in color, and contained thin greenish-brown fluid in which there was considerable fine, soft brown material. This fluid contained no trypsin and only a trace of amylase (activity of 10). From it were cultured *B. coli* and gram-negative cocci. The liver was swollen. The common duct was widely dilated above the ligature and normal below it. There were several large lymph nodes.

Microscopic Findings.—Gallbladder: The epithelium was partially gone and the wall much thickened with edema and somewhat infiltrated with polymorphonuclear and mononuclear leukocytes. Common duct: This presented the same findings as the gallbladder. Pancreas and kidneys: Normal. Liver: There was an increase in interstitial fibrous tissue and this tissue contained bile pigment. There were many areas of collections of polymorphonuclear cells and areas of necrosis of liver cells.

GROUP V.—*Permanent Obstruction Distal to the Juncture of the Pancreatic Duct Plus Cholecystostomy*

Goat No. 9.—Approx. age, one month. *Diagnosis:* Subacute cholecystitis.

The common duct was permanently ligated distal to its juncture with the pancreatic duct, and a cholecystostomy was performed, with a catheter draining the gallbladder to the exterior. The catheter was extruded seven days later; an autopsy was performed on the following day.

Gross Pathology.—There was considerable digestion of the skin for a wide area around the drainage tube. This became apparent within 24 hours after operation and was progressive. The gallbladder was buried in adhesions and was contracted. Its wall was thick and was grayish-white in color. The pancreas and liver were normal in appearance and the extrahepatic ducts were not distended.

Microscopic Findings.—Gallbladder: The wall was much thickened with edema of all layers but mainly of the serosa. There was also considerable lymphocytic infiltration and an increase in fibrous tissue. Pancreas: Normal. Liver: Slight interstitial edema.

Goat No. 10.—Approx. age, one month. *Diagnosis:* Subacute cholecystitis.

Cholecystostomy only was performed. The ducts were not disturbed. Aspirated gallbladder bile contained no traces of any enzymes and was sterile on culture. The animal was killed and autopsied eight days later.

Gross Pathology.—The gallbladder and sinus tract were buried in adhesions. The gallbladder was contracted and its wall was thick and injected. The liver, pancreas, and extrahepatic ducts were normal in appearance. Regional lymph nodes were enlarged. There was only slight erosion and digestion of the skin around the drainage sinus.

Microscopic Findings.—Gallbladder: The wall was thickened by edema (mainly of the serosa) and by a marked lymphocytic infiltration and increase in fibrous tissue. The tissues also contained some polymorphonuclear leukocytes. The epithelium was hyperplastic. Pancreas: Normal. Liver: Normal.

Goat No. 11.—Approx. age, one month. *Diagnosis:* Subacute cholecystitis.

The common duct was permanently ligated distal to the juncture of the pancreatic duct, and the gallbladder was drained externally by means of a catheter. Aspirated gallbladder bile contained a trace of amylase, and no bacteria on culture. Death occurred six days later; no definite cause for it could be demonstrated.

Gross Pathology.—The gallbladder was buried in adhesions and was thick-walled and contracted. The extrahepatic ducts were not dilated. The pancreas appeared to be congested and the liver normal. Regional lymph nodes were enlarged.

Microscopic Findings.—Gallbladder: The wall was much thickened with edema, fibrosis and infiltration with lymphocytes and polymorphonuclear leukocytes. The cellular infiltration was mainly submucosal. The epithelium was hyperplastic. Pancreas: The ducts were dilated and the blood vessels were distended. The gland was otherwise normal. Liver: Essentially normal. Kidneys: Essentially normal.

Goat No. 21.—Approx. age, 15 months. *Diagnosis:* Acute gangrenous, nonperforated cholecystitis with bile peritonitis.

The common duct was ligated distal to the juncture of the pancreatic duct and a cholecystostomy was performed, draining the gallbladder to the exterior through a catheter.

Gallbladder bile procured at time of operation was negative for trypsin but positive for lipase and amylase (activity of 10). Microscopically, it was negative and gave no growth on culture. Bile aspirated from the tube 24 hours later contained both trypsin (activity of 2.0) and amylase (activity of 160), 40 leukocytes and 100 red blood cells per H.P.F., and gave no growth on culture.

Aspirated bile, five days after operation, contained both trypsin (activity of 2.2) and amylase (activity of 140). Smears presented only amorphous material and crystals. Cultured were *B. coli* and gram-negative cocci.

The tube fell out on the eighth day and drainage immediately ceased. The animal began to fail rapidly and was killed and autopsied three days later, 11 days after operation.

Gross Pathology.—There had been considerable digestion of the skin around the sinus. The abdomen contained 600 or 700 cc. of bile stained fluid, and the peritoneal surfaces were slightly inflamed. This fluid contained both trypsin (a trace) and amylase (activity of 20), and was negative on culture. The gallbladder was distended, edematous, opaque, and grayish-white. Vessels on the surface were dilated. There was no demonstrable perforation of the gallbladder or leakage from the sinus. The gallbladder bile contained both trypsin (activity of 1.8) and amylase (activity of 140), and from it were cultured *B. coli* and gram-negative cocci. The extrahepatic ducts were moderately dilated.

Microscopic Findings.—Gallbladder: The wall was thick, very edematous and partially necrotic. The mucous surface was almost entirely devoid of epithelium and the wall was moderately infiltrated with lymphocytes and contained a few polymorphonuclear leukocytes. Liver: Normal. Pancreas and kidneys: Tissue lost.

Group VI.—*Spontaneous Cholecystitis*

Goat No. 15.—Approx. age, 14 months.

Upon exploration, this animal was found to have developed a cholecystitis spontaneously. Consequently no experimental procedure was undertaken. The animal was immediately autopsied.

Gross Pathology.—The gallbladder presented a few adhesions, was normal in size, and was dull red in color. Surface blood vessels were dilated. The wall was moderately thickened. The common duct was slightly dilated. Both gallbladder and ducts contained normal bile. The gallbladder bile contained amylase (activity of 20) and a trace of trypsin. Cultures yielded *B. coli.*

Microscopic Findings.—Gallbladder: The wall was moderately thickened, the epithelium slightly hyperplastic in some areas, absent in others, and there was some edema and moderate lymphocytic and fibroblastic infiltration. Common duct: This showed similar changes. Pancreas and kidneys: Normal. Liver: Considerable fatty degeneration.

BRIEF ANALYSIS OF RESULTS OF EXPERIMENTS

Since the common duct in goats acts as a common conduit for both bile and pancreatic secretions, pancreatic juice normally is constantly present in the proximal end of the common duct. It would appear, therefore, that under normal conditions pancreatic juice either does not enter the gallbladder or if it does, it is innocuous. In an endeavor to investigate this question the gallbladder bile of five normal goats was examined for pancreatic enzymes. In three, traces of trypsin and lipase were found, and in all, small amounts of

amylase. Since many tissues of the body contain amylase, its presence in the gallbladder bile has no particular significance. It has been shown by several investigators that pancreatic juice is innocuous until the enzymes have been activated by some substance. Consequently unactivated enzymes could conceivably be present in the gallbladder without causing damage. Thus, there is good evidence that pancreatic juice becomes a pathogenic factor in gallbladder disease only as a result of some other factor (probably stasis) which causes this juice not only to enter the gallbladder but also to become activated within this viscus.

Quantitative determinations were made of amylase by the method of Myers and Fine, and of trypsin by the method of Gross. Only qualitative determinations were made of lipase.

Since the experimental results varied with respect to the site of obstruction produced in the common duct, the duration of the obstruction and the age of the experimental animals, the discussion is presented under the following headings.

I. OBSTRUCTION DISTAL TO PANCREATIC DUCT

The common duct was obstructed distal to the juncture of the pancreatic duct in 15 animals. The obstructions in seven were permanent, and in eight temporary.

(1) *Permanent Obstruction.*—No animal survived obstruction longer than 11 days. Three died within 26 hours. The three that lived five days or longer showed evidence of jaundice.

At postmortem examination, there was found, without exception, enormous dilatation of the gallbladder, cystic and hepatic ducts, and of the common duct above the site of obstruction (Fig. 4). In five animals the gallbladder and ducts were adherent to the duodenum and other adjacent tissues and there were edema and very large lymph nodes in the gastrohepatic omentum.

In four goats (Nos. 2, 4, 7 and 8) there was present a bile peritonitis with no demonstrable perforation in the wall of the distended gallbladder and ducts. Microscopically, the tissues of the walls of these gallbladders were either partially or entirely necrotic (Fig. 5A). In two there was no inflammatory reaction, while in one there was moderate edema and in another much infiltration with lymphocytes and polymorphonuclear leukocytes.

In one goat (No. 1), the gallbladder had perforated with formation of a small abscess containing bile. The wall of this gallbladder was very thick, opaque, grayish-white in color, with dilated vessels on its surface. It was moderately edematous and extensively infiltrated with both mononuclear and polymorphonuclear leukocytes. There were also areas in which the tissue was necrotic. In the other two goats (Nos. 5 and 13), there was considerable edema, particularly in the serosa, and in one considerable infiltration with inflammatory cells. In all animals the epithelium was entirely missing or present only as small remnants in the depths of the folds.

The gallbladder bile in all seven animals contained both amylase and

trypsin. It was sterile in three (Nos. 2, 4 and 5), and contained *B. coli* and gram-negative and -positive cocci in four (Nos. 1, 7, 8 and 13). There was also present much débris which had the appearance of digested blood.

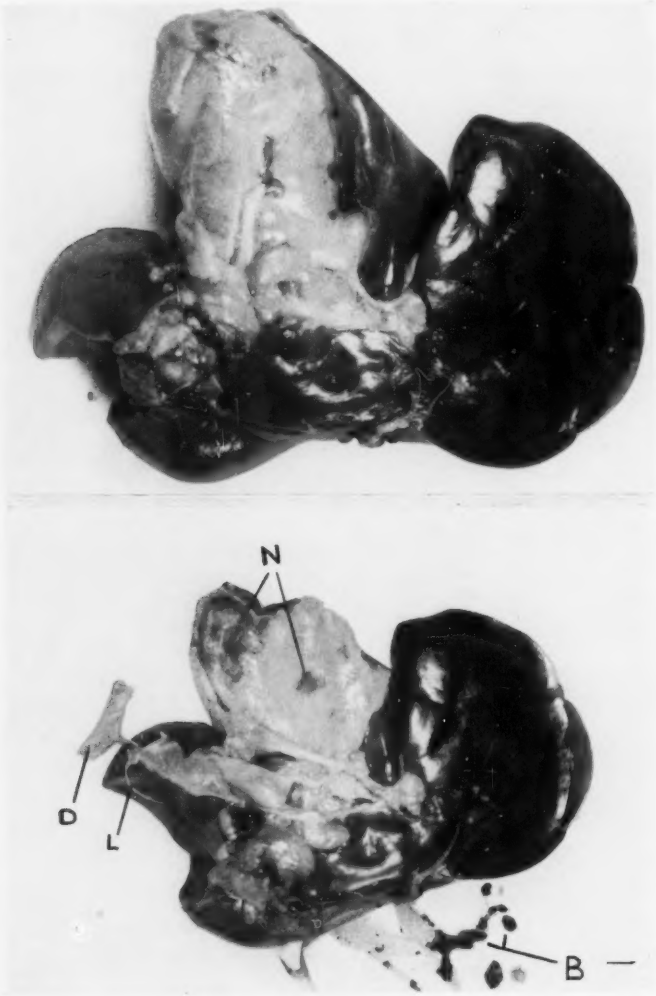


FIG. 4—A: Enormous distention of the gallbladder resulting from obstruction of the common duct below the duct of Wirsung in Goat No. 14. This same degree of distention resulted from obstructions above, as well as below, the juncture of the duct of Wirsung. Note edema, adhesions and lymphadenopathy.

B: The gallbladder and ducts opened. (D) Duodenum. (L) Obstructing ligature with common duct much dilated above and normal below it. Note (N), areas of hemorrhage and necrosis in the wall. (B) Débris in gallbladder bile consisting of blood, necrotic tissue and inspissated bile.

Two goats were yearlings and five were approximately one month of age. In the two older animals the liver, kidneys, and pancreas were normal.

In the five infants, there were gross and microscopic findings of acute pancreatitis with digestion necrosis in four (Fig. 5C). The pancreatic ducts

were dilated in all five, and bile was seen in the ducts in three (grossly in two, and microscopically in one [Fig. 5B]). The liver in three of this group contained multiple small abscesses.

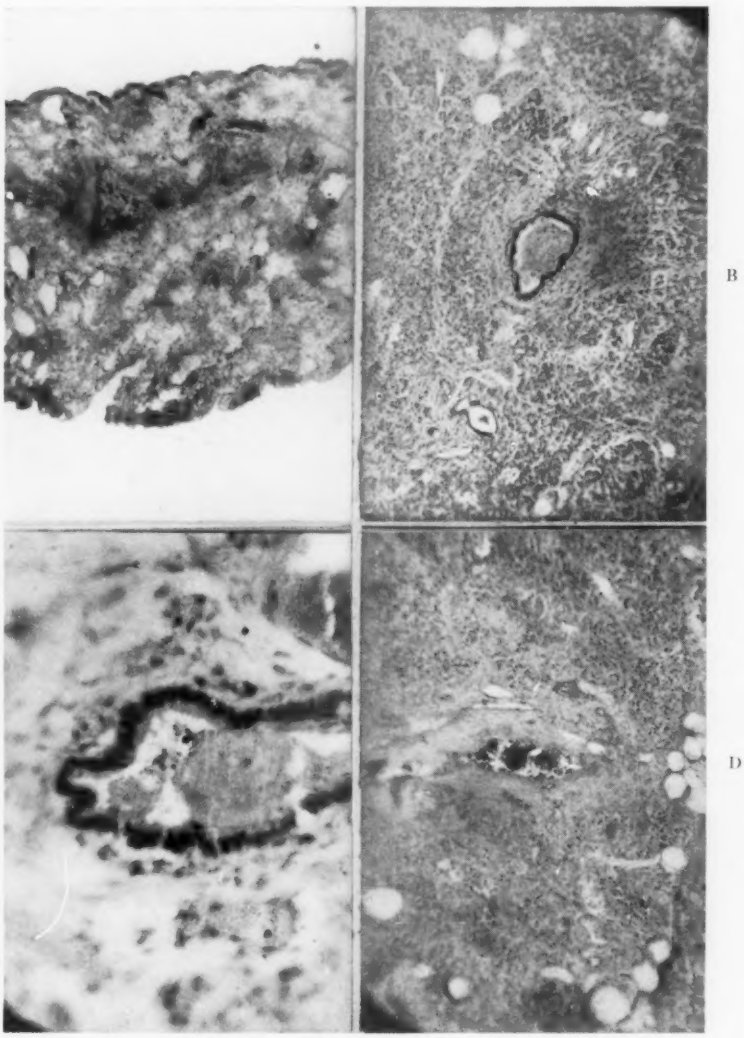


FIG. 5.—Goat No. 4: Obstruction of the common duct distal to the juncture of the duct of Wirsung for three days produced gangrenous cholecystitis and pancreatitis with peritonitis.

A: Wall of gallbladder shows edema and aseptic necrosis. Note absence of lining epithelium, also absence of lymphocytic and leukocytic infiltration.

B and C: Area of pancreas showing a dilated duct filled with bile, with beginning necrosis of the acinar tissue around it.

D: Another area of pancreas showing necrosis of all tissues including necrosis of fat within the pancreas.

COMMENT.—It should be emphasized that (a) all gallbladders in this group contained pancreatic enzymes, evidence of hemorrhage into the viscus and loss of epithelium; (b) there was no evidence of infection in three;

(c) there was complete or partial gangrene of the wall of the gallbladder in five out of seven, with bile peritonitis in four and perforation in one; (d) the pancreas was unaffected by obstruction in the two older animals, and definitely damaged in the five infants (dilation of ducts in five, presence of bile in the ducts in three, and acute pancreatitis in four).

(2) *Temporary Obstruction:*—It was found in the first group of goats used in this study, as reported above, that the very young ones developed acute pancreatitis in addition to cholecystitis, and died promptly after obstructing the distal end of the common duct. This did not occur in the two older ones of the group. Obviously, therefore, to study the effect of temporary obstructions the older animals had to be used. Consequently, all were four months and older. In two animals the distal end of the common duct was obstructed with a ligature of plain catgut, so that the duration of obstruction was not definitely known. In six, the obstructions were produced by the method illustrated in Figure 3 and were maintained from one to six days.

The two goats (Nos. 14 and 16), in which catgut ligatures were used, died from the results of the obstruction 19 and 32 days later. The ligatures had resulted in the formation of strictures which had caused persistence or recurrence of obstruction. Both had extreme dilatation of the gallbladder and biliary ducts above the sites of obstruction, which was complete in one and nearly complete in the other one. The wall of the gallbladder in both was much thickened with edema, and the bile contained both trypsin, and amylase, and *B. coli* and gram-negative and -positive cocci. In the one which was four months of age, there was an acute, nonperforated gangrenous cholecystitis, with bile peritonitis, and acute pancreatitis with digestion necrosis. In the older one, 14 months of age, there was a perforation of the gallbladder, which was partially necrotic, and an adjoining abscess containing the same character of fluid as that found in the gallbladder.

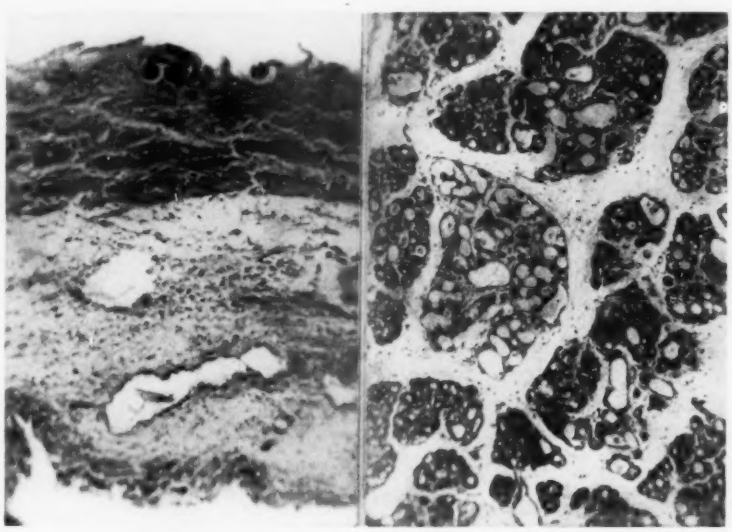
A third goat (No. 22), in which the common duct was obstructed for six days, died two days after the obstruction was released. Although bile could be expressed from the ampulla by squeezing the gallbladder, both gallbladder and bile ducts were considerably distended. Gallbladder bile contained both trypsin, amylase, and *B. coli*. The wall of the gallbladder was almost entirely necrotic but contained a few fibroblasts.

The remaining five goats (Nos. 17, 18, 19, 20 and 24) lived with apparent good health, and were killed six months after the common duct had been temporarily obstructed. Three of them were explored four weeks after the original operation, and bile obtained by aspiration. It contained débris, crystals and white and red blood cells in addition to both trypsin and amylase. In one, it was sterile and from the bile of the other two, *B. subtilis, B. coli,* and gram-negative and -positive cocci were cultured. At postmortem examination, the gallbladders of all five goats were extensively adherent to the duodenum and other tissues, and presented edema, fibrosis and lymphocytic infiltration of the walls in varying degrees. The wall in four (Fig. 7), was very thick and opaque, with dilated vessels on the surface, and in one, it was fairly thin and

partially translucent. The lining epithelium was hyperplastic in three, and in one of these there was a papilloma. In two, the surface was devoid of epithelium in many areas.

In all five animals the gallbladder bile was normal in appearance, but in each instance *B. coli* was cultured from it or from the wall of the gallbladder. The bile contained only amylase, and in small amount, in the two specimens examined.

In three (Nos. 19, 20 and 24), of the five gallbladders, bile pigment stones were present. The stones in two animals were numerous and very small, and



A B

FIG. 6.—Goat No. 13: In this animal, obstruction of the common duct distal to the juncture of the pancreatic duct for six days produced acute cholecystitis with only partial necrosis of the wall.

A: Gallbladder wall shows much edema, mainly of serosa, and some lymphocytic infiltration; also dilated vessels and loss of most of the lining epithelium. In contrast to Figure 5, there is only partial necrosis of tissues.

B: The pancreas presents markedly dilated ducts and acini but no necrosis; also edema of interlobular connective tissue. On gross examination, bile was observed in the duct of Wirsung.

were present in both the gallbladder and the dilated common duct. The other gallbladder contained three stones, two of which were very small and one fairly large. Two of these specimens are shown in Figure 8.

In all of the animals, the pancreas and kidneys were normal and the liver normal except for slight fatty degeneration.

In every instance the common duct was greatly dilated despite the fact that there was no apparent obstruction and bile flowed freely into the duodenum. Contrary to the observations reported by Brackertz, the common duct in these animals showed the same pathologic changes found in the gallbladder.

COMMENT.—Three animals in this group died of acute, gangrenous cholecystitis, one complicated by acute pancreatitis. In two, there developed a latent stenosis of the distal end of the common duct. Both pancreatic enzymes and infection were present in these gallbladders.

Five goats developed chronic cholecystitis with infection, and in three, stones formed.

(3) *Permanent Obstruction with Cholecystostomy.*—In each of three goats (Nos. 9, 11 and 21), two, approximately one month of age, and one, about 14 months old, the distal end of the common duct was ligated with silk but, in addition, the gallbladder was drained through a catheter extending just beyond the skin surface. Bile aspirated at the time of operation was sterile on

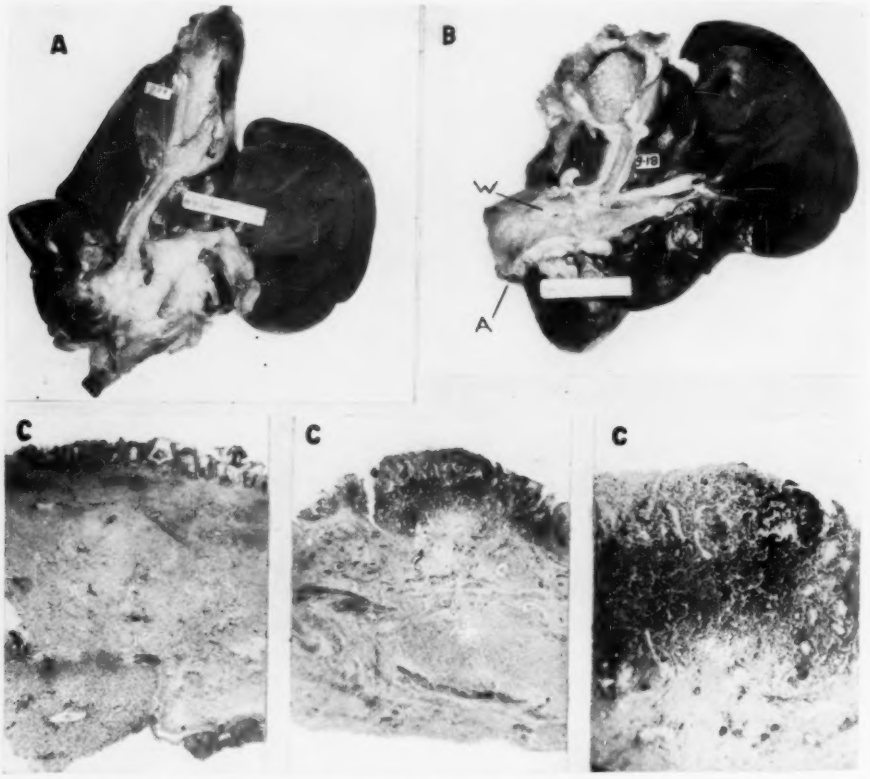


FIG. 7.—Goat No. 18: Chronic cholecystitis six months after a temporary obstruction of the common duct distal to the juncture of the duct of Wirsung.

A: Gross specimen. Note the thick, opaque wall of the gallbladder, with engorged surface vessels, dilated cystic and greatly dilated common ducts.

B: The gallbladder and ducts opened. Note the thick wall of the gallbladder and the enormously dilated common duct. (W) Indicates the duct of Wirsung and (A) the ampulla of Vater.

C: The wall of the gallbladder is thick, showing some edema, fibrosis, regenerated epithelium and extensive infiltration with lymphocytes (especially subepithelial). These sections taken from two areas of the wall show the histologic variation.

culture and contained only traces of amylase. In one animal (No. 21), samples of bile were collected aseptically 24 hours, and five days, after operation. Both specimens contained trypsin in addition to large quantities of amylase. In the first specimen there were 40 leukocytes and 100 red blood cells per H.P.F., and no bacteria on culture. The specimen obtained on the fifth day contained amorphous material, crystals and *B. coli* and gram-negative cocci on culture. This animal subsequently died with an acute, nonperforated gangrenous

cholecystitis, with bile peritonitis which followed three days after tube fell out and drainage ceased.

In all three animals, the skin for a considerable distance around the wound became raw, presumably digested. This excoriation undoubtedly resulted from the action of pancreatic enzymes. This contention is supported by the fact that very little excoriation took place in a fourth animal (No. 10) which had a cholecystostomy without obstruction of the common duct. Drainage without obstruction was established in this animal for purposes of comparison. Grossly and microscopically, the gallbladder in this animal did not differ from that of two in which drainage was supplemented by obstruction of the common duct. In all of them, the gallbladder was contracted and the wall was very thick with edema, mainly of the serosa. It was infiltrated with lymphocytes, polymorphonuclear leukocytes and fibroblasts, and the epithelium was not only intact but appeared to be hyperplastic.

COMMENT.—Although pancreatic enzymes traversed three of these gallbladders, in only one (No. 21) was there loss of epithelium and necrosis of the wall such as occurred in the previous group of animals in which obstruction of the common duct was not decompressed by drainage of the gallbladder. In Goat No. 21, however, the drainage sinus closed, with the result that the obstruction was no longer decompressed and stasis with distention followed. Thus, it appears that pancreatic enzymes are activated and attack the wall of the gallbladder only in the presence of stasis or that the wall becomes vulnerable only when it is distended. The pathologic changes found in the two contracted gallbladders were the result, no doubt, of trauma and infection.

OBSTRUCTION PROXIMAL TO PANCREATIC DUCT

The common duct was obstructed proximal to the juncture of the pancreatic duct and distal to the juncture of the cystic duct in five goats. The obstructions were made permanent in one animal with a ligature of silk, and temporary in four.

(1) *Permanent Obstruction:*—The one goat in this group (No. 12) was one month of age. It died nine days after obstruction was established. There was a definite jaundice which was apparent in the tissues. The gallbladder and the ducts above the ligature were enormously distended. The gallbladder bile contained no trypsin and only a trace of amylase. *B. coli* and gram-negative cocci were cultured from it.

The walls of the gallbladder and common duct were edematous and infiltrated with mononuclear and polymorphonuclear leukocytes. It was partially devoid of epithelium but there was no necrosis of the other tissues of the wall. The liver contained focal areas of necrosis and multiple abscesses. The pancreas was normal.

COMMENT.—Stasis in this animal accompanied by infection resulted in acute cholecystitis, hepatitis, and multiple liver abscesses. There was, how-

ever, no necrosis of the wall of the gallbladder and no pancreatitis as occurred with obstructions below the pancreatic duct in goats of this age.

(2) *Temporary Obstruction:*—The four goats (Nos. 24, 26, 27 and 28) were approximately one month of age. The duration of the obstructions was 24, 48, 72, and 144 hours, respectively. The animal which was obstructed for 24 hours died from a respiratory infection five days later. The others were killed while apparently in good health, 14 days after the operation.

With the exception of Goat No. 27, which will be discussed separately, the gallbladder, ducts, pancreas, and liver of each animal were essentially normal, both grossly and microscopically (Fig. 9). There were, however, in each

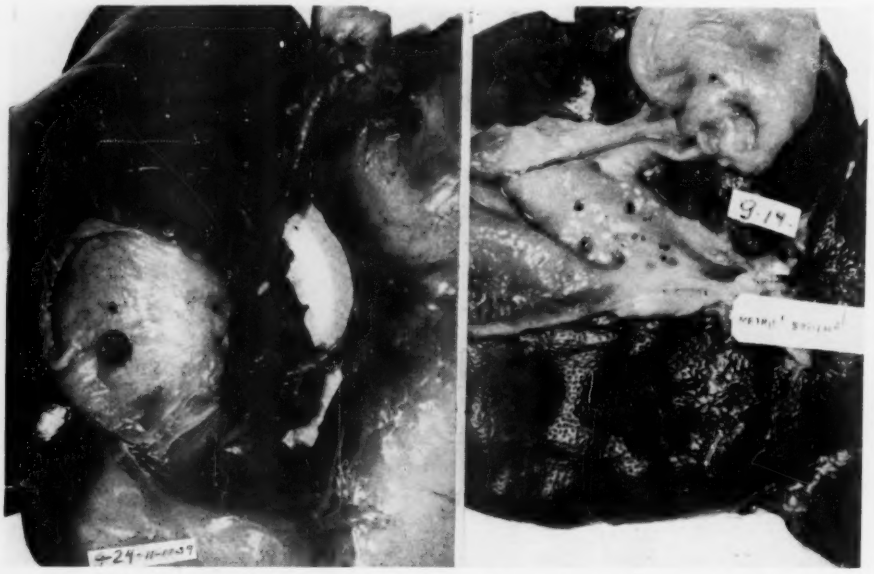


FIG. 8.—Chronic cholecystitis with cholelithiasis which developed several months after temporary obstruction of the common duct distal to the juncture of the pancreatic duct in Goats Nos. 24 and 19. Note enormous dilatation of common duct and stones in both duct and gallbladder of Goat No. 19.

animal some pericholecystic adhesions, and adhesions between the duodenum and common bile duct. In each instance, the common duct was patent but was narrowed and its wall thicker than normal at the site where temporary obstruction had been applied. The gallbladder bile was normal in appearance and contained only amylase. It was sterile on culture in two goats and gave a growth of pneumococcus in one.

In Goat No. 27, an obstruction was maintained for six days, and the subsequent fibrosis of the wall of the duct at the site where obstructions had been applied had resulted in stenosis which was almost complete. Above this level the common duct and the hepatic and cystic ducts were much distended as was the gallbladder. The gallbladder bile was normal in appearance and contained only amylase. From it were cultured the staphylococcus (possibly a contaminant) and a diplococcus. The liver was swollen and the intrahepatic ducts dilated. The wall of the gallbladder was thicker than normal, the lining epi-

thelium intact and normal, and there was no necrosis of tissue. The subepithelial tissues were moderately edematous and densely infiltrated with lymphocytes. The pancreas was normal. The gross and microscopic appearances of this gallbladder are shown in Figure 10.

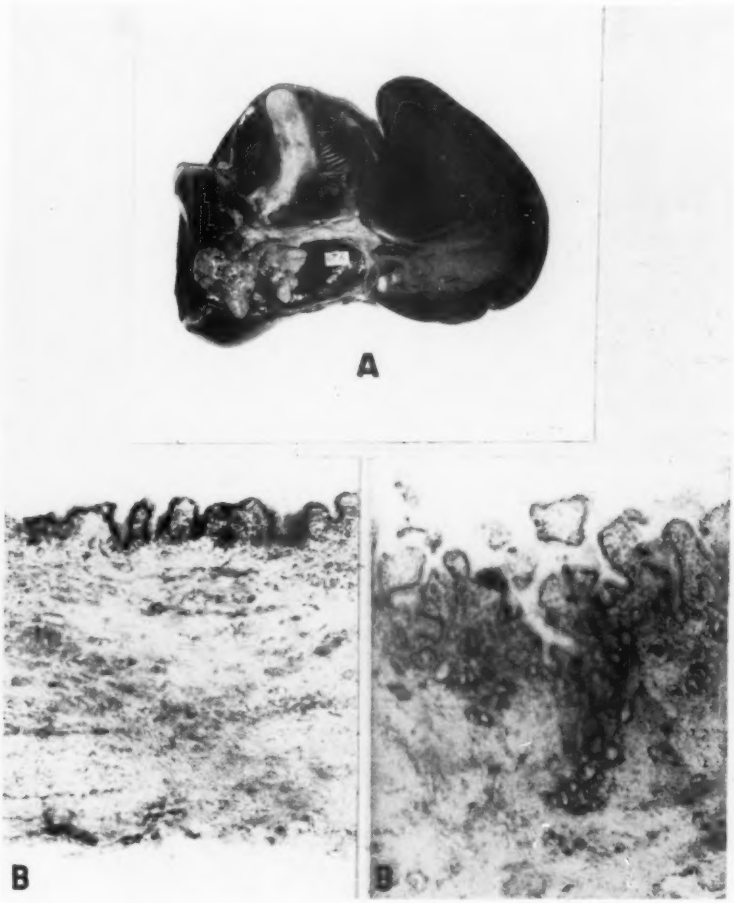


FIG. 9.—Goat No. 26: The common duct was obstructed for 48 hours proximal to the juncture of the pancreatic duct and distal to the cystic duct. The animal was killed 12 days later.
A: Gross specimen showing an essentialy normal gallbladder.
B: Microscopically, also, the wall of the gallbladder is essentially normal. Temporary biliary stasis produced no permanent damage.

COMMENT.—The gallbladders of animals in this group were subjected to temporary stasis of bile without the reflux of pancreatic secretions. With the exception of the one animal, in which partial obstruction persisted, there was a return of the biliary tract to an essentially normal condition. There was no loss of epithelium or necrosis of the wall such as occurred in gallbladders subjected to the reflux of pancreatic juice in addition to stasis. The pancreas was unaffected.

III. NATURAL CHOLECYSTITIS

In the course of the investigation one of the yearling goats (No. 15) presented, at operation, a gallbladder with the gross appearance of cholecystitis. *B. coli* was cultured from the wall of the gallbladder. The findings were essentially the same as those of the experimentally produced chronic cholecystitis with the notable exceptions that there were no pericholecystic adhesions and no dilatation of the common bile duct. The ducts and liver were normal in appearance and no mechanical explanation for the cholecystitis could be found.

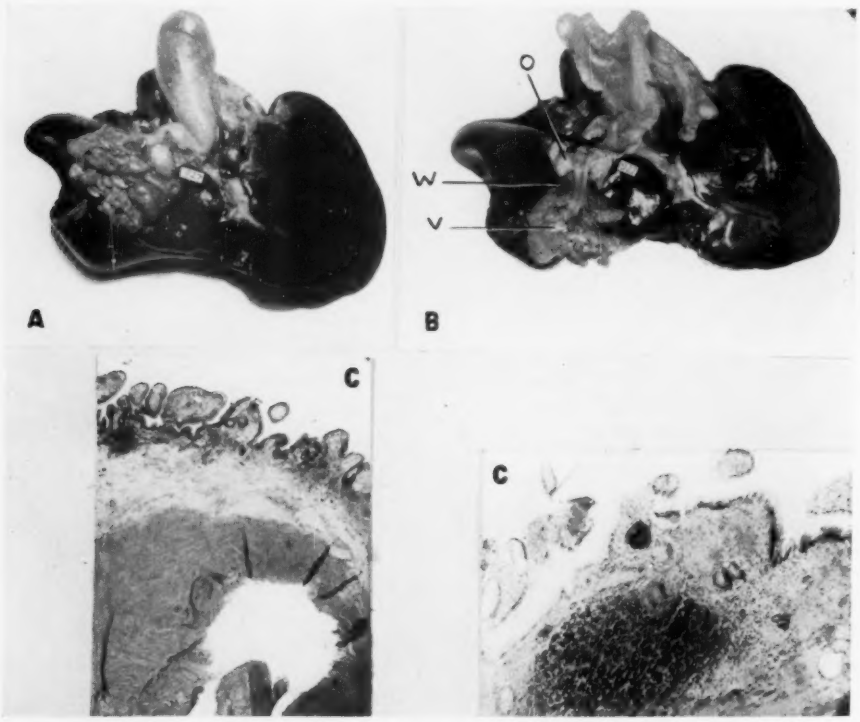


FIG. 10.—Goat No. 27: Common duct was obstructed for six days proximal to the duct of Wirsung and distal to the cystic duct. Scarring at site of obstruction resulted in partial permanent stenosis.

A and B: Gross specimen shows moderate distention of the gallbladder and of the ducts proximal to the area of stenosis. (O) Site of obstruction; (W) juncture of duct of Wirsung; (V) ampulla of Vater. Note that the common duct below the stenosis is normal.

C: The wall of the gallbladder shows moderate edema and much lymphocytic infiltration of the subepithelial tissues. Despite prolonged biliary stasis, the lining epithelium is intact and normal, and there is no necrosis of the tissues as resulted from obstructions distal to the juncture of the duct of Wirsung. This gallbladder was infected: cholecystitis resulting from stasis plus infection.

DISCUSSION AND CONCLUSIONS

From these experimental data it may be concluded that neither stasis of bile nor the reflux of pancreatic juice as a single factor was productive of cholecystitis. When combined, they invariably produced permanent pathologic changes in the gallbladder. By their combination, there was produced acute aseptic cholecystitis with complete or partial necrosis of the wall of the gallbladder. The immediate pathologic changes, it is believed, were chemically

induced and not the result of infection, for the reasons that they lacked histologic features characteristic of infection and that cultures from the gallbladder bile and wall were sterile in most instances. In several animals there was an associated bile peritonitis without perforation of the wall of the gallbladder and, in two, a perforation with localized peritonitis. Precisely the same pathologic pictures occur in man, and we share the conviction of Wolfer that the pathogenesis is the same.

In the older animals, which survived this initial acute reaction, which we have reason to believe included some necrosis of the wall of the gallbladder, there developed chronic gallbladder disease not unlike that of man. No gallbladder subjected temporarily to both stasis and reflux of pancreatic secretions reverted, with recovery, to its previous normal condition. All developed permanent pathologic changes. Despite the fact that the mucous membrane completely or partially regenerated in most instances, evidence of chronic inflammation persisted. Since bacteria were cultured from all of these chronically inflamed gallbladders, it seems probable that superimposed infection was an important contributing factor in this subsequent development of chronic cholecystitis.

Unquestionably, the bile pigment stones, which developed in three animals, formed as an indirect, if not direct, result of stasis and reflux of pancreatic secretions. In addition to precipitation from altered relations of the chemical constituents of the bile, these gallbladders contained much débris, consisting of blood from hemorrhage and of fragments of sloughed mucous membrane. Theoretically, these particles provided nuclei around which precipitated elements could collect. This débris, always present in the bile for a few weeks after the initial insult from stasis and pancreatic reflux, gradually disappeared, and the bile became clear and normal in appearance.

Temporary biliary stasis alone (in absence of pancreatic reflux) had no destructive action upon the wall of the gallbladder and was productive of permanent pathologic changes in only those gallbladders in which there were positive cultures to indicate that infection had supervened. In the absence of infection, gallbladders subjected to temporary stasis promptly reverted to their previous normal states.

Thus, it may be concluded that stasis played an essential and fundamental rôle but not the active one in the production of cholecystitis and stones. Apparently it merely created circumstances favorable to the damaging activity of pancreatic enzymes and of bacteria. In other words, cholecystitis resulted from stasis plus either the reflux of pancreatic secretions or infection or a combination of the three factors.

The same factor which induced stasis caused the reflux of pancreatic juice, and, in turn, distention of the gallbladder. Thus stasis either activated the pancreatic enzymes or, by distending the wall of the gallbladder, rendered it vulnerable to the action of the enzymes and to infection. It is our belief that these same factors are responsible for chronic cholecystitis in man.

In our animals, stasis was induced by obstructing the common duct. There

is much evidence that temporary obstruction of the common duct in man may result from spasm of the sphincter of Oddi and from reverse peristalsis in the duodenum, in addition to stones or other obstructing factors within the common duct or at the ampulla.

The occurrence of acute pancreatitis in five of the younger goats, following obstruction of the common below the pancreatic duct, was an interesting incidental development. The pathogenesis of acute pancreatitis has been attributed to the reflux of bile into the pancreas with the assumption that the bile activates the pancreatic enzymes within the pancreas itself. This contention, however, has been contested by some contrary evidence. Thus, it has been shown by Harms and Dragstedt that in the dog the secretory pressure of the pancreas is greater than that of the liver. It has been reasoned that under these circumstances it is unlikely that bile would enter the pancreas. This begs the question of relative secretory pressures to explain the presence of bile in the pancreas, and the development of pancreatitis in the very young goats and the failure of its development in the older ones. It is probable that, in the former, the secretory pressure of the liver exceeded that of the pancreas. In two of the very young goats the presence of bile in the pancreatic ducts was observed grossly and, in one, microscopically.

It has been shown that filtered bile does not activate pancreatic enzymes but that bile unfiltered or containing bacteria does. This may serve to explain the absence of pancreatitis in one of the goats in which bile could be seen in the pancreatic duct. But it also seems reasonable to assume that the refluxed bile observed in the pancreas of the other two goats was a pathogenic factor in the production of acute pancreatitis in these animals.

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DISCUSSION.—DR. CHARLES P. BAKER (Omaha, Neb.): Doctor Bisgard has shown you the gross pictures of the livers and gallbladders taken from our animals, and I wish briefly to discuss the microscopic findings which we have in these animals.

The first group is the one in which the ligature was temporarily placed above the duct of Wirsung and so we have only the bile obstruction. In part

of these animals the bile was sterile and in part cultures grew streptococci. Sections of the gallbladder walls in this group show collections of leukocytes in the subepithelial region and edema of the wall. There was no evidence of necrosis of the wall in this group.

In the second group of animals the ligature was placed below the pancreatic duct and the animals were killed in two to three days following the procedure. In these animals the gallbladder wall was digested, and sections show no structure remaining normal in the wall. There were no collections of leukocytes in the wall and the mucous membrane was entirely gone. In part of these animals the pancreatic sections showed bile in the pancreatic ducts and there was digestion of the pancreatic acini and fat in many areas. Apparently the ferments for fat and protein digestion had been activated. The picture of the pancreas is similar to that which we see clinically in so-called acute pancreatitis. The liver in a number of these animals had small abscesses distributed throughout its substance.

In the third group of animals the common duct was temporarily ligated below the pancreatic duct and the animals were killed several months later. In this group of animals the epithelial lining of the gallbladder mucosa was intact. The walls in this group were thickened by edema and fibrosis, and there were uniformly present large collections of leukocytes in the subepithelial region of the wall. It was in this group of animals that calculi were found in several instances.

DR. JOHN A. WOLFER (Chicago, Ill.): I am indeed pleased to hear this report by Doctor Bisgard because, December 5, 1930, I presented the results of some experimental work on this subject before the Chicago Surgical Society. It did not seem to impress anyone present at that meeting; in fact, I could not convince my audience that the theory had any merit whatsoever. Since that time, however, it has gained proponents.

Recently, I made a survey of the literature reporting the results of anatomic studies on the relationship of the terminal common duct to the pancreatic duct. It indicates that in eight studies covering 652 cases, a common pathway between the pancreatic and common ducts was found in 43.4 per cent of cases. This would indicate that in approximately 45 per cent of all individuals there is a common pathway between the pancreatic and common ducts, thus allowing an interchange of duct contents; *i.e.*, bile to pass into the pancreatic system and pancreatic juice into the biliary ducts and gallbladder. Many cholangiograms, when carefully studied, reveal a visualization of the pancreatic ducts as stated by Doctor Bisgard. We are able to verify this observation.

For our experimental work we used the dog, placing a cannula into the major pancreatic duct and a T-tube into the common duct. These two were connected externally, using a glass observation bulb so as to be able to determine whether the preparation was satisfactory. Since the secretory pressure of the pancreas is greater than that of the liver, the flow in a successful preparation was always from the pancreatic to the biliary side, revealing a turbid opalescent fluid in the observation bulb. In order to determine whether the pancreatic juice that was flowing into the common duct ever entered the gallbladder, India ink was introduced into the observation bulb in one animal. Five days later the animal was explored and the mucosa of the gallbladder was found stained black as were also the contents of the gallbladder.

Aside from the preparation just described, we injected pancreatic juice directly into the gallbladder; also into the common and cystic ducts in some of the experimental animals. Figure 1 shows the gallbladder of an animal 24 hours after the injection of 15 cc. of pancreatic juice into the cystic duct.

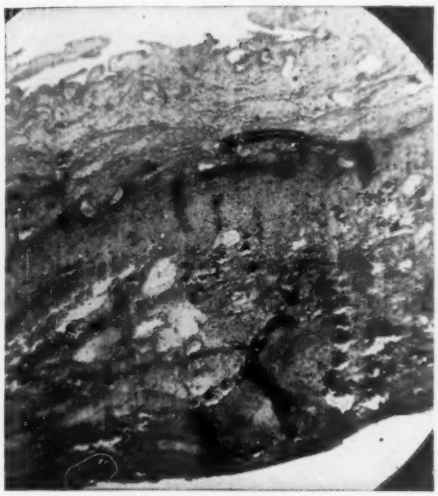

FIG. 1.—Photomicrograph (×35) of the wall of the gallbladder of a dog that died 24 hours after the injection of 15 cc. of pancreatic juice into the cystic duct. The wall is much thickened, 4Mm., and shows diffuse necrosis, with edema. No viable structures can be seen. (Courtesy of Surgery, Gynecology and Obstetrics.)

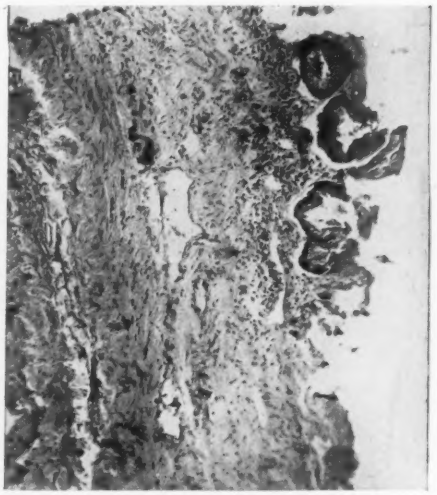

FIG. 2.—Photomicrograph (×85) of the gallbladder wall of a dog that was killed 20 days after the injection of 20 cc. of pancreatic juice into the gallbladder. The mucosa has partly sloughed away. There is shown extensive infiltration of inflammatory cells into the submucosa and muscular layers, and infiltration and thickening of the serosa.

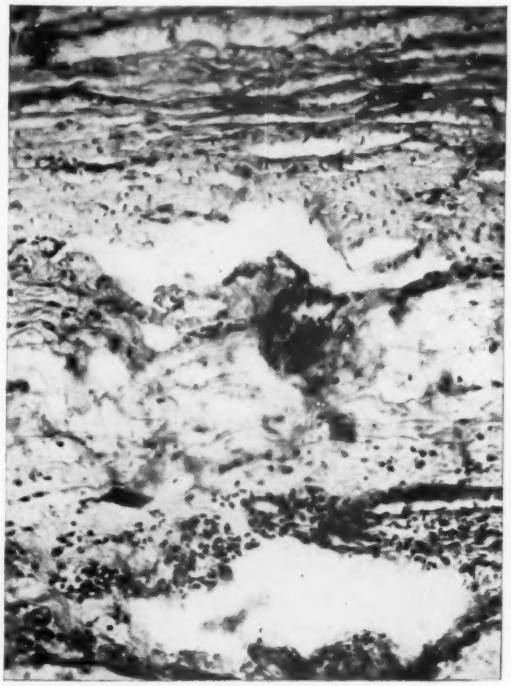

FIG. 3.—Photomicrograph (×195) of the serosa of the gallbladder of a dog that died seven days after a choledochopancreatic intubation. On the left can be seen a dilated blood vessel with perivascular infiltration. There is present extensive necrosis, with edema, and some cellular infiltration.

The gallbladder was gray in color and the wall 4 Mm. in thickness. There was complete necrosis of the wall, with edema. No viable structure or cells could be seen. Such a response was encountered on several occasions, the process often being associated with bloody bile stained fluid in the peritoneal cavity.

With the introduction of pancreatic juice into the biliary duct system or gallbladder, varying pathologic changes were found in the wall of the gallbladder of the individual cases. In a case in which 20 cc. of pancreatic juice had been injected into the gallbladder, 20 days later a study of the gallbladder revealed a partial sloughing away of the mucosa with an infiltration of inflammatory cells into the remaining portions of the mucosa, the submucosa and muscular layers (Fig. 2). The microscopic appearance of the wall of the gallbladder is almost identical with one that Doctor Bisgard has shown. In another instance in which the animal died seven days after a choledochopancreatic intubation, there was found extensive necrosis, with edema; also cellular infiltration with perivascular infiltration in the wall of the gallbladder (Fig. 3). In every instance that the experiment was successful, pathologic changes were found in the wall of the gallbladder ranging from acute and extensive necrosis to partial necrosis and regenerative hyperplastic changes. The longest time interval observed was in an animal killed 187 days after a choledochopancreatic intubation had existed for nine days. There were found hypertrophy and hyperplasia with retention cyst formation and extensive inflammatory cell infiltration of the mucosa of the gallbladder (Fig. 4).

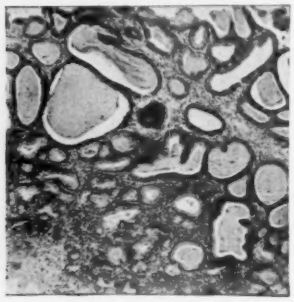

FIG. 4.—Photomicrograph (×45) of the mucosa of the gallbladder of a dog killed 187 days after a choledochopancreatic intubation had flowed nine days. There are shown hypertrophy and hyperplasia with cyst formation, and extensive inflammatory cell infiltration.

There seems to be no question, at least not in my mind, that pancreatic juice reflux may explain many of the bizarre pathologic pictures frequently observed in the operating room. My curiosity was aroused, in 1928, when I encountered a large, tense and cyanotic gallbladder in the presence of an acute pancreatitis. The gallbladder was removed and, much to my surprise, cultures from the walls of the gallbladder and its contents were sterile. It was obvious that there must be some unrecognized process at work, a process not infectious in nature, that was the basis of the profound changes found. That observation led to the experimental work that was reported ten years ago. I am indeed pleased to see the results of Doctor Bisgard's work upon the same subject and quite naturally I am gratified by his conclusions.

DR. EVARTS A. GRAHAM (St. Louis, Mo.): I think this has been a most interesting paper, beautifully presented. I am not quite certain, however, whether Doctor Bisgard wishes to give the impression that all cases of cholecystitis are due to this mechanism or only a small percentage of them. I have been interested in Doctor Wolfer's ideas on this subject ever since he proposed them, and I would say that I think that the idea is a very attractive one. I should like to feel that the explanations are as simple as Doctor Wolfer and Doctor Bisgard, now, would have us believe. On the other hand, there are certain things that, from a purely logical standpoint, make it difficult for me to accept this idea as an explanation of many cases of cholecystitis.

These ideas, briefly, are: In the first place, this idea would make the origin of cholecystitis due to an anatomic anomaly which presumably exists

from the time of birth or even in fetal life, if you will. Pancreatic secretion becomes active in late fetal life. How does it happen, then, that children—babies—who have this deformity escape cholecystitis if it is due merely to this anatomic arrangement; and why is it, therefore, that cholecystitis is a disease of middle life, or beyond, almost entirely? Now, again, Doctor Wolfer calls our attention to the fact that approximately 45 per cent of people have this anatomic arrangement; but 45 per cent of the people do not have severe cholecystitis—or any way near that percentage!

Again, Doctor Bisgard introduces the element of stasis as an important factor. Of course, Aschoff has, for many years, emphasized the importance of stasis as a factor in the production of cholecystitis. I am not sure whether or not Doctor Bisgard means obstruction when he speaks of stasis. That is, of course, a very different thing, namely, obstruction is a very different thing from stasis. Now, as a matter of fact, people who have stasis in the gallbladder are the type of individuals who are less likely to have cholecystitis. "Uncle Sam" does not have cholecystitis, but "John Bull" does. By cholecystography, one can demonstrate that "Uncle Sam" has stasis but "John Bull" does not. The individual with the long gallbladder is the one who has stasis; and frequently this gallbladder is to be seen, by cholecystography, not to empty for 36 or 48 hours. The patient who has gallbladder disease is the one who has the cholecystographic shadow that appears as a circle up under the ribs. "John Bull" I mentioned. Heavyweight wrestlers and pugilists represent types of individuals who are likely to have gallbladder disease. Yet they empty more promptly than what we consider the normal gallbladders; therefore, it is difficult for me to understand, really, that the explanation of cholecystitis can be so simple as this idea which is proposed and promulgated this morning by Doctor Bisgard, which he would have us believe.

Now I am pleased, however, I must say, to see this additional evidence in favor of the idea that cholecystitis is not, by any means, always an infectious process. I used to think that it was, but I think that the evidence is becoming more and more overwhelming that it is not.

There is another point which I think is interesting to consider in connection with this presentation. It is not a question of: Can you produce cholecystitis by getting pancreatic juice into the gallbladder? Anyone would accept that. I cannot see that there would be any doubt about that, but the point is, of course, does human cholecystitis, as we see it, occur in this way? Now you can produce cholecystitis by introducing lots of things into the gallbladder. Mann showed, many years ago, that an intravenous injection of Dakin's solution resulted in a gangrenous cholecystitis, but certainly he did not mean to imply that human cholecystitis is caused by people going around getting intravenous injections of Dakin's solution; and that is, Mr. President, the enigma which it seems to me these studies present.

DR. J. DEWEY BISGARD (Omaha, Neb., closing): There is a very strong growing feeling that infection is not the initial etiologic factor in the majority of the cases of cholecystitis. It has been shown, of course, and repeated experimentally by Andrews and many others, that it is practically impossible to infect the normal gallbladder. They have introduced various types of bacteria into the gallbladder and have failed to initiate an infection unless the gallbladder was also damaged or had been previously damaged. So we believe that the physical or chemical changes that took place in the presence of stasis in these animals damaged the gallbladder wall and rendered it vulnerable to either bacteria or enzymes. Now we are not attempting to apply these observations directly to the disease in humans, but we can show in our animals,

subjected to stasis alone, that the gallbladder returned to a fairly normal condition. Stasic gallbladders that did not become infected returned to normal. If they became infected, they developed the picture of subacute or chronic cholecystitis.

It has been demonstrated repeatedly, particularly by Colp in a large series of cases, that one can frequently recover pancreatic enzymes from the gallbladder. I think he recovered them in as many as 20 per cent of the cases in which the common duct was drained, showing that the mechanism can take place. As to the frequency with which it takes place, I have no idea. I do believe, however, that it is the mechanism responsible for most of the cases of acute gangrenous cholecystitis that we see.

THE QUESTION OF DRAINAGE FOLLOWING CHOLECYSTECTOMY*

IRVIN ABELL, M.D.

AND

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THE WIDE DIVERGENCE of opinion regarding the wisdom or even the propriety of omitting drainage after cholecystectomy due to reported instances of bile leakage with resultant peritonitis, has led us to review a series of 500 consecutive cases subjected to operation during the decade from 1930 to 1940. For purposes of brevity and facility of discussion cholecystectomy alone, carried out in the absence of surgical attack upon other portions of the biliary tract or adjacent organs, other than the coincident removal of the appendix, will be considered. The questions upon which decision is sought are: Is it permissible to eliminate drainage; and is it always necessary to drain even after "ideal cholecystectomy"?

In our earlier experience, drainage by a rubber tube or a plicated strip of gauze enclosed in rubber tissue, designated as a "cigarette drain," was employed in all cases. Undesirable sequelae following such practice were occasionally noted, and consisted chiefly of infection, delay in wound healing, and persistence of sinuses for days beyond the time required for the healing of the undrained wounds. We finally came to the practice of discarding drainage in cases conforming to certain criteria, and it is to this group to which we invite your discussion.

It has been our practice to employ drainage in every case showing gangrene; marked pericholecystic edema, inflammation or abscess; demonstrable common duct and pancreatic disease; spillage of bile from the gallbladder or cystic duct; the visible presence of bile in the beds of the gallbladder and cystic duct; abnormal relationship of artery, vein and ducts which do not permit of satisfactory identification and control; and in the instances in which the separation of pericholecystic adhesions has left appreciable denuded surfaces. It is our belief that the drain employed in the presence of these indications—tube, cigarette or Penrose—should be left *in situ* for a time sufficiently long to permit of canalization that will insure a route of exit for wound secretions and discharges; a period of time which our experience indicates to be not less than six or seven days. The practice of removing the drain piecemeal at intervals of 24 to 48 hours has, at times, resulted in retention and accumulations in the depth of the wound, permitting the occurrence of that which their employment was designed to prevent and materially prolonging convalescence. The employment of drainage in the conditions

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mentioned is so universal as to require no further comment, but when one approaches the elimination of drainage in "ideal cholecystectomies" opinions and practices show divergence.

The wide variations in the anatomic relations of the cystic artery and duct, hepatic artery, portal vein, common and hepatic ducts have been repeatedly described; and the presence of accessory ducts in relation to the cystic and hepatic ducts as well as ducts of embryonal origin in the perimuscular coat of the gallbladder has been noted. Flint, in an article upon the "Abnormalities of the Right Hepatic, Cystic and Gastro-Duodenal Arteries, and of the Bile Ducts," in the British Journal of Surgery of April, 1923, reported finding accessory hepatic ducts in about 15 per cent of his dissections. The ducts of Luschka found on the perimuscular hepatic surface of the gallbladder, which while not communicating with the gallbladder do often anastomose with the bile ducts in the liver, have been estimated by some to be present in 6 per cent of all cases.

The above findings, together with reported failures of closure of the cystic duct after ligation, offer to many surgeons an imperative demand for the employment of drainage in every case. Is the surgical importance of these anomalies overestimated by some and underestimated by others? Are these anatomic variations susceptible of recognition at operation? Is there a technic which gives any assurance of such recognition, at the same time affording a degree of safety in occluding aberrant and accessory ducts? Instances of drainage from the stump of the cystic duct as late as six to eight days after ligation have been observed. Do these bear any relation to the method of ligation or to the degree of pressure or infection in the common duct, and are there any reliable criteria upon which security of obliteration or of danger of reopening may be predicated? Beyond the generally accepted indications for the employment of surgical drainage elsewhere, these are the problems about and upon which hinges the choice for or against drainage following cholecystectomy.

Briefly, the "ideal cholecystectomy" we have in mind, and in which we have eliminated drainage, is presented by the case in which the common duct is normal in size and gives no evidence of concretions or periductal inflammation; in which the head of the pancreas shows no increase in size or consistence; in which the relations of the cystic duct, the common duct and the cystic artery can be readily defined by dissection with satisfactory identification of each; and in which the gallbladder can be separated from its bed by sharp dissection without exposure of liver tissue. In such instances the cystic duct, with or without the cystic artery, depending upon their relations, has been doubly ligated with No. 1 chromic catgut ligatures—one, a transfixion ligature placed proximal to the clamp in which the duct is held; the other, a mass ligature at the site of the grasp of the clamp. The connective tissue bed of the gallbladder is closed by a continuous suture of chromic catgut welded on a curved intestinal needle, beginning at the point of ligation of cystic duct and proceeding to the outermost point of the gallbladder bed,

after which it is carried back to its starting point, transfixing the tissues not tightly held in the first layer. In this technic no liver tissue is exposed and the cellular tissue of the gallbladder bed is firmly closed. We have at times covered the stump of the cystic duct with peritoneal flaps, as a rule, however, omitting this feature without noting any difference in convalescence.

Of the 500 cases reviewed, 109 were drained and 391 were not drained. Acute cholecystitis was present in 74; chronic and subacute, in 426. Calculi were present in 408, absent in 92. Of the acute cases, 34 were drained and 40 not drained. Of the chronic and subacute, 75 were drained and 351 not drained. There were ten deaths in the series, a mortality of 2 per cent, two occurring in the 109 drainage cases, and eight in the 391 nondrainage cases.

Bronchopneumonia alone accounted for five deaths—two on the third, one on the fourth, one on the fifth, and one on the twelfth postoperative day. The patient dying on the fifth day presented a marked ileus, arousing the suspicion of an intra-abdominal etiology independent of the toxemia from the pulmonary lesion. Autopsy revealed the peritoneal cavity free of pathology.

Dehiscence occurred in two cases: One, not drained, exhibiting persistent singultus, beginning on the third postoperative day, developed a dehiscence on the thirteenth day, and died of a terminal bronchopneumonia on the seventeenth day; the other, drained, developed a primary bronchopneumonia, and suffered a dehiscence on the fifth day, and died on the eighth day. Both abdomens, at time of resuturing, were free of evience of leakage or of peritonitis.

One patient died of acute hepatic toxemia after removal of a gangrenous gallbladder. One died of mesenteric thrombosis, symptoms appearing on the tenth, exploration being made on the eleventh, and death occurring on the twelfth postoperative day: permission for autopsy was refused, the origin of the thrombosis remaining conjectural. The tenth fatality occurred on the third postoperative day as a result of myocardial failure and pulmonary edema.

In our earlier experience, a cigarette drain was the one commonly employed; bile-tinged drainage during the first 24 to 72 hours was occasionally noted. In the present series, employing a more meticulous technic, and using a Penrose tube as a drain, bile-tinged drainage, in scant amount, has rarely been observed. All of the patients analyzed in this series were private ones, and since many of them elected to remain in the hospital for a longer time than was actually necessary, no accurate estimate of the required hospitalization can be given for the two groups. It is our impression, however, that the Penrose drain increases the time of hospitalization in but few instances.

Our experience in this series, as well as in that of previous years, leads us to believe that the anomalies of the cystic artery and of the bile ducts do not have the surgical significance which has been accorded them by some observers. While we believe that the reported cases of such anomalies demand a particularly careful operative technic in all instances, we are by no means sure that the one we employ gives complete assurance against leakage from

unrecognized accessory ducts or reopened cystic ducts. We are not so optimistic as to believe that what has happened to others may not happen to us. The presence of infection in the common bile duct may not always be recognized by inspection and palpation, and, when present, may be the cause of failure of obliteration of the cystic duct with consequent leakage. We may have been fortunate in relying upon the criteria mentioned in protecting us from such a disaster. In any event, we have not seen, in this series or in the experience of previous years, any of the complications which have been ascribed to closure without drainage. The valid arguments which may be offered in favor of the elimination of drains are the avoidance of adhesions which their presence necessarily engenders, and the occasional delay in wound healing induced by infection, with prolongation of convalescence and resultant weakened scars. That such advantages do or do not outweigh proven dangers, and as to whether or not in selected cases a careful technic offers a reasonable margin of safety in avoiding the latter, is to be proved by collective rather than individual experience.

DISCUSSION.—DR. JOHN A. WOLFER (Chicago, Ill.): I am indeed happy to hear Doctor Abell present his thesis at this meeting. We have for years, in the group I work with, omitted drainage in the majority of cases following cholecystectomy. The question seems to revolve about the possibility of leakage from the cystic duct which is ligated at the time of operation; therefore, infection and sundry other aspects need not be considered at this time.

In 1927–1928, in order to determine what happens to a ligated cystic duct, we carried out some experimental work upon the dog. It may be pertinent to mention again the results of that work, since it has a direct bearing upon the subject before us at this time.

It was noted that 24 hours after operation, the stump of the cystic duct was covered with an exudate consisting of red blood cells and coagulated serum, so that it was not visible after the lobes of the liver and other adjacent structures that had prolapsed over it had been separated. Microscopic examination of the duct stump revealed compression of the tissues within the grasp of the ligature and beginning cellular disorganization of the stump, distal to the ligature. At the end of four days, the exudate containing many young connective tissue cells was well fixed to the duct stump, completely covering it. When the exudate was separated from the duct stump, it was noted, very frequently, that the ligated duct was very brittle, so that it would fracture at the site of ligation with the slightest brush with the tip of the finger; revealing an open lumen without any evidence of repair. Microscopic examination of the duct stump showed necrosis of the duct wall distal to the site of ligation, under the ligature, and for a few millimeters proximal to it; proximal to this, the duct wall appeared normal (Fig. 1). This would indicate that the ligature deprived the duct wall of its blood supply, since the portion of the duct under the ligature, and distal to it, had been dissected free at the time of ligation and the only blood supply available was that within the wall of the duct. The cystic duct wall does not repair itself as does a blood vessel by a reparative process within the duct wall, as can be noted in Figure 1. By the end of seven days, the exudate is firmly fixed to the duct structures and can be separated only with difficulty. Microscopic examination of the exudate shows many young and maturing connective tissue cells. Examination of the duct stump clearly indicates the site of ligation and complete necrosis distal and

a few millimeters proximal to the site of ligation. It also illustrates the absence of any reparative process within the duct wall so that a disruption at the site of ligation, at this time, will lead to a communication between the lumen of the proximal duct and the exterior (Fig. 2).

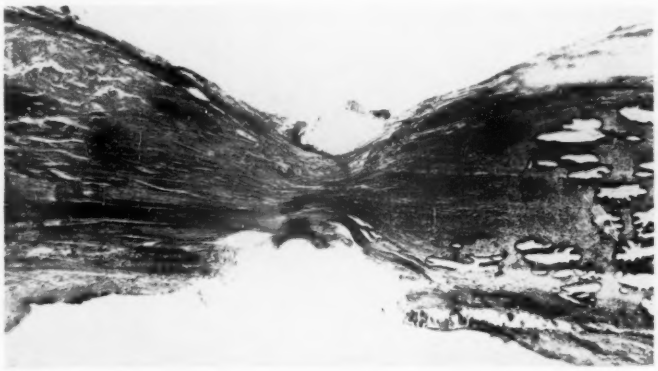

FIG. 1.—Photomicrograph of the cystic duct stump at the zone of ligation on the fourth day. This shows the zone of proximal as well as distal necrosis. (Low power)

As this process is followed along, it can be noted that the exudate finally becomes well organized, and completely obliterates the duct stump by burying the necrotic portions in a mass of well-organized connective tissue. This was observed at the end of 33 days.

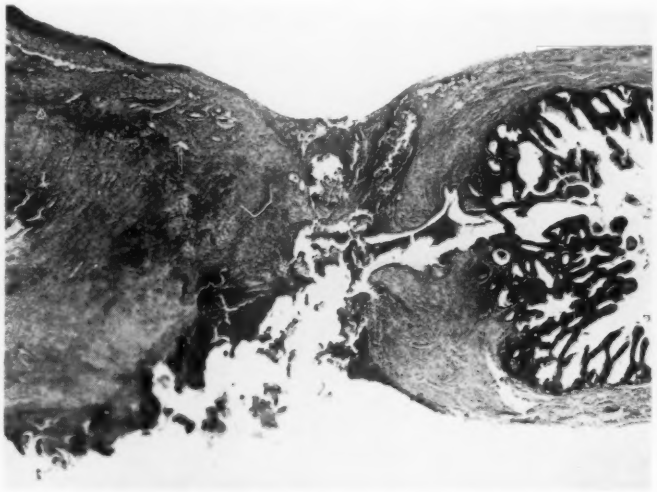

FIG. 2.—Photomicrograph of the cystic duct stump on the seventh day. This clearly indicates the extensive necrosis distal to the ligature, also beneath and proximal to the ligature; and demonstrates that, at this period, no reparative changes have taken place in the duct to occlude its lumen.

It was also noted, in the experimental animals into which we inserted drains, that if anything was placed about the cystic duct stump that interfered with the deposition or laying down of the exudate, which later became the defensive and reparative mechanism, healing was prevented or markedly delayed. If drains were inserted and then removed on the third or fourth day,

the exudate which had already formed around the duct was disturbed and did not cover the stump, so that a definite time-interval had to elapse for a further, and sometimes inadequate exudate to form, thus interfering with and delaying repair.

It would seem that this experimental work warrants the conclusion that in those cases in which there is no reason for drainage other than a fear of leakage from the cystic duct, it is distinctly contraindicated. We employ drainage following cholecystectomy very, very rarely; I would say in not more than 5 per cent of our cases, and, so far, we have had no reason for regrets.

DR. HENRY F. GRAHAM (Brooklyn, N. Y.): I have believed for many years in the general principle that it is better to omit drainage in operations upon the gallbladder whenever possible but have carefully avoided any attempt to influence others to adopt this practice because of the obvious dangers of closing the abdomen without a drain when one is necessary. It now seems fair, however, to give our statistics. Over a period of about ten years, we have accumulated a series of consecutive cases without drainage. There have been 346 in all, with 12 deaths, or a mortality of 3.47 per cent. Please note that these are not consecutive cases, but they are consecutive cases which were *not* drained. In the last 200 gallbladder operations, up until March 12, 1940, no drain was employed in 62.5 per cent, or, conversely, we drained one-third of the cases.

It is our belief that none of the deaths occurred as the result of lack of drainage. Postoperative accumulation of bile did occur in two cases but both of these recovered. Closure of the abdomen without a drain does diminish postoperative pain; gives more prompt and better healing of the wound; and favors the deep breathing which we all so much desire following gallbladder operations.

I agree with Doctor Wolfer that the insertion of a drain is often responsible for the biliary discharge which is sometimes seen in a wound and which the surgeon says is positive proof that a drain was needed. If the drain were not inserted, the tissues would collapse and you would get peritoneal exudate and adhesions, as he mentioned; and you would not have biliary discharge at all.

In considering these statistics which I have mentioned, if they seem high to you at all, I should like to remind you that we have an active ambulance service at the Methodist Hospital. We serve a large tenement house district with many Italians. This may affect our mortality somewhat.

DR. HARRY B. ZIMMERMAN (St. Paul, Minn.): I was very much interested in Doctor Abell's presentation and also in Doctor Wolfer's experimental work. If you will notice in Doctor Wolfer's last slide there is a canalization of the cystic duct. This section was taken five or six days after the ligature had been applied. If one considers the abdomen as a closed hydrostatic bag, then all pressures, at any one time, would be equal, and leakage from a viscus would occur only when the pressure within the viscus compared to pressure without the viscus was great enough to rupture its wall. If the differential pressure were always the same, this would not take place.

Years ago, when we used rigid tubes, we made the atmosphere communicate directly with the weakest part of the duct. Consequently, we nearly always had bile leakage. At present, when one uses a Penrose drain, the closed container is not sufficiently spoiled, so that leakage is not so likely to occur; but should the drain be left in long enough, so that its tract becomes thoroughly canalized with a rigid inflammatory wall, the tube situation will

again obtain, and there will be a point of positive differential pressure at the end of the canal at a time when the duct wall was weakest and rupture of the duct could very well occur. Should there be a diastasis of the muscular abdominal wall six days after operation, the same situation would occur. Should there be positive pressure throughout the entire abdomen, except in the neighborhood of the hernia, leakage would occur.

Therefore, in the operation for removal of the gallbladder, in order to prevent bile leakage it is important to have accurate closure of the abdominal wall by means of an incision so designed as to make a hernia least likely—and no drain! If there is a possibility that one may get an early hernia and a leakage of bile, obviously it is best to have a fistula.

I would say the ideal situation is a ligated duct and a closed abdomen. If there is any doubt about this, use a drain that could establish a fistula but, also, that it should be so placed, and the abdominal wall sutured about it so tightly, that the closed container is not spoiled and that there is the least likelihood of a differential pressure at the point at which the duct was ligated.

Dr. Charles G. Mixter (Boston, Mass.): I should like, briefly, to call attention to the value of immediate cholangiography in determining the safety of closure without drainage. Perhaps the most potent cause of leakage is back pressure through the cystic duct from impediment to the outflow. If a renal catheter is placed in the cystic duct, the valve is obtained in withdrawal of bile, and one can determine whether or not a cholangitis exists. Secondly, if the common duct is visualized and immediate, free flow into the duodenum is demonstrated, one is quite sure that the element of back pressure due to impediment of the outflow of the bile into the duodenum is eliminated. I believe that in that selected group where some of us feel we can close the abdomen without drainage, cholangiography at the operating table gives us an added factor of safety.

NEUROGENIC DISTURBANCES OF THE COLON AND THEIR INVESTIGATION BY THE COLONMETROGRAM*

A PRELIMINARY REPORT

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IN 1927, Rose[1] described a method of observing the reaction of the bladder to filling. Many communications of interest have appeared since, which have been recently reviewed in McLellan's[2] excellent monograph. Cystometry has become a most useful aid in studying the behavior of the bladder. Eight years before Rose's first publication, Joltrain, Baufle, and Coope[3] proposed a method of measuring the filling pressure of the large intestine. They described only a few such attempts and drew no important conclusions. So far as we are aware, nothing more had been done in studying the physiology of the colon by colonmetry until the method was independently rediscovered and put into routine use in the study of neurologic disturbances in defecation at the Massachusetts General Hospital, two years ago.

METHOD.—The apparatus employed is very simple, and consists of a vertical glass tube manometer one meter in height, connected on one side to an intravenous drip apparatus and on the other to a rectal tube (Fig. 1). The reservoir is filled with water at body temperature and the tubing cleared of air. The base line of the manometer is adjusted so that the meniscus of the water column is at the zero mark when the tip of the rectal tube is level with the patient's anus. The tube is then inserted a few inches within the rectum and held in this position by adhesive tape. It is best to have the patient lying on his back with his head comfortably supported on a pillow. When the anal sphincter is paralyzed the connection can be made water-tight by using a Foley bag type of catheter with the balloon inflated to 100 cc. (Fig. 1, insert). The same device is also useful when the test has to be made through a colostomy opening. Once the apparatus is adjusted, water is allowed to flow into the rectum at a constant rate of approximately 100 cc. per minute. The patient is instructed to report any sensation of "gas," "urge to defecate," or cramp-like pain, with its location and intensity. Extreme care must be exercised in any patient with an insensitive colon or with colonic diverticula, lest a perforation be produced by overdistention.

The test is best performed a number of hours after the last meal and when

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the bowel has been recently evacuated. A correct interpretation cannot be drawn if the patient has been given a cathartic or narcotic drug.

We wish to point out that the colonmetrogram does no more than measure the tone, reflex irritability, and sensitivity of the colon as a whole. It gives a good indication of the competence of the anal sphincter, but fails to give a true

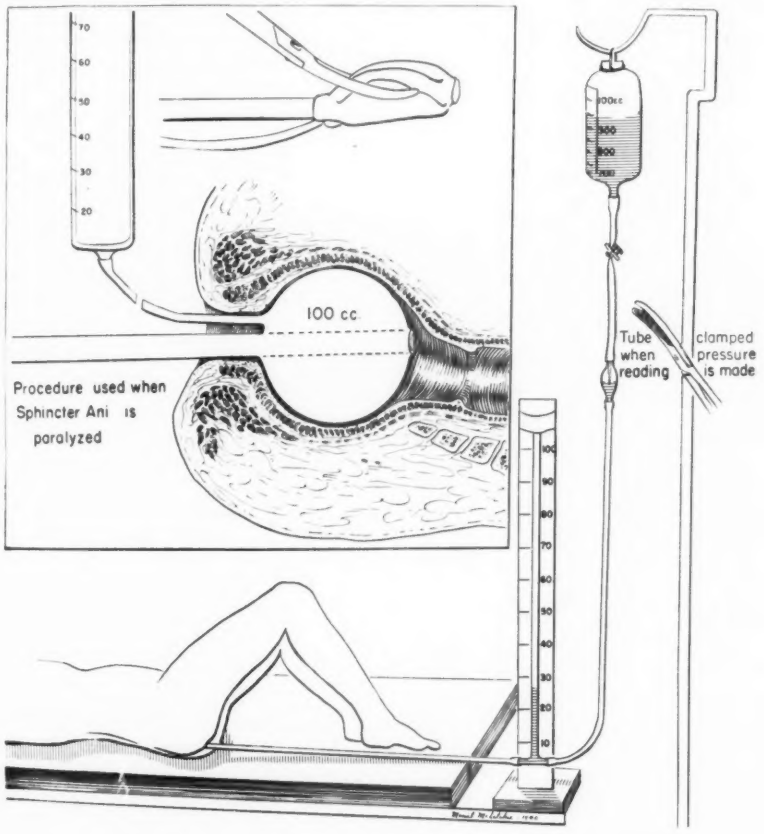

FIG. 1.—Apparatus and technic of colonmetry.

indication of the expulsive power of the rectum, which is dependent to a large degree on the contractile force of the abdominal musculature and the diaphragm. The integrative mechanism of the rectum, sphincter ani, and perineal muscles must be studied by the more elaborate methods which have been described by Denny-Brown and Robertson.[4] Furthermore, localized functional abnormalities in the rectum, sigmoid, or higher portions of the colon cannot be differentiated. It would appear, however, that neurologic disturbances usually affect the colon as a whole, and for this reason we have found the colonmetrogram to be a simple and valuable method of testing the nervous activity of the viscus.

MATERIAL.—This investigation has been focused on patients with disease, injury, or operative lesions of the brain, spinal cord, cauda equina, or pelvic

nerves which may cause an alteration of function or sensation in the large bowel. Sixty-seven colonmetrograms have been performed in a series of 40 patients.

RESULTS.—The normal colonmetrogram closely resembles the cystometrogram, except for the fact that a fourfold larger volume of water is usually required for filling.* Figure 2 illustrates the comparative volume of fluid which is required to fill the normal bladder and colon. Whereas the normal adult bladder holds from 300 to 500 cc. at a maximal comfortable capacity, the colon holds between 1,500 and 2,000 cc. Both hollow viscera have

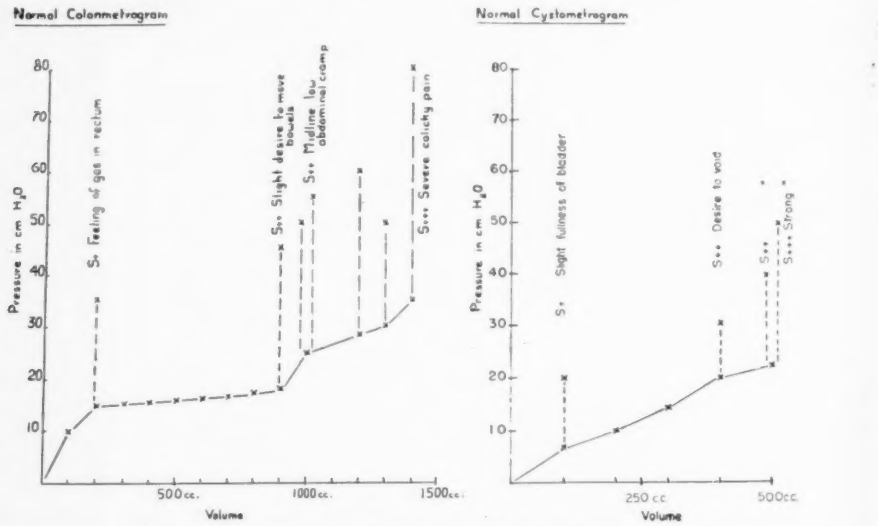

FIG. 2.—The normal colonmetrogram and cystometrogram.

a relatively similar basic tone and react to stretching by intermittent reflex attempts to empty. This is shown by peristaltic contractions which last a few seconds and send the intravesical and intracolonic pressures up to from 30 to 90 cm. A sensation of fulness is produced in the normal colon, as in the bladder, when the pressure reaches 30 cm., whereas a contraction which raises the column above 50 cm. becomes distinctly uncomfortable. The basic tone is seen to rise rather steeply as the normal capacity is approached, and peristaltic waves occur with increasing frequency until a state of tetanic contraction is reached. At this point, fluid usually leaks out around the catheter. The pressure-volume measurements can be combined with barium fluoroscopy if a thin barium mixture is used that will not clog the manometer. The contraction peaks are then seen to correspond to mass waves of peristalsis which sweep the fluid down into the distal colon. Haustral segmentation does not produce any waves visible in the manometer, as no fluid is forced down the canal.

* With slow filling of the colon there is always a possibility of leakage through the ileocecal valve. Short of fluoroscopic examination, this unknown factor cannot be controlled, but we have no evidence that it is of importance.

The smooth muscle in the colon, as in the bladder, reacts to stretch stimuli by reflex contraction (Denny-Brown and Robertson[4]). Colonmetry in patients with various types of neurologic lesions, therefore, brings out changes which are characteristic of the level at which the nervous system is involved. These phenomena are identical with those observed in the bladder (McLellan[2]), and quite similar to alterations in the tendon reflexes.

Typical cases which illustrate the effect of injury to the various segmental levels of the nervous mechanism of defecation are appended. It must be borne in mind that this is a preliminary report and that colonmetry has not been

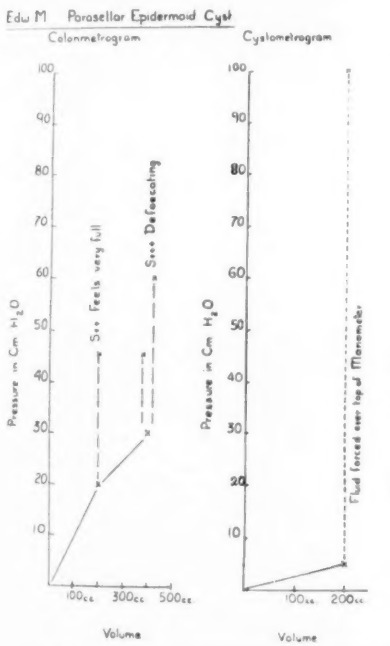

FIG. 3.—Case 1: Hypertonia of colon and bladder seen in the case of a brain tumor which compressed the hypothalamus and cerebral peduncles.

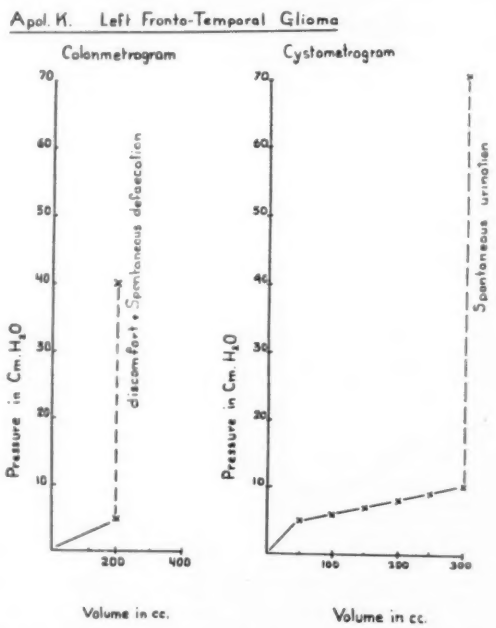

FIG. 4.—Case 2: Hypertonia of colon and bladder observed in an extensive tumor of the left frontal lobe.

undertaken on a large enough series of cases to draw final conclusions. But the evidence at hand is entirely consistent and the findings quite similar to data obtained from the bladder by a great many investigators. Since conclusions can be drawn only from complete and clearly defined lesions of the nervous system, such as can be produced in the experimental animal, this report is necessarily based upon the relatively small proportion of our total cases which fulfill these criteria.

I. LESIONS IN THE BRAIN

Case 1.—Edward M., male, age 15. Epidermoid cyst in floor of left middle fossa, with extension across the midline and compression of hypothalamus and cerebral peduncles (verified at autopsy).

The patient was intelligent and cooperative. There was no clinical evidence of injury to the autonomic centers in the hypothalamus. Both his cystometrogram and colonmetrogram curves are reproduced in Fig. 3, and reveal an extraordinary hypertonicity of both bladder and colon, with entirely normal sensation. On a second occasion, the colonmetrogram was repeated with barium and the filling observed fluoroscopically. On account of the intense muscular activity of the sigmoid, barium could not be forced up beyond the rectosigmoid.

Case 2.—Apol. K., male, age 57. Left frontotemporal glioma. Diagnosis was established only by ventriculography, as the patient subsequently died without operation or postmortem examination.

The patient was aphasic, apraxic, and had undergone a pronounced change in personality, so that his cooperation could not be counted on with certainty. Right hemiparesis and a suggestive homonymous field defect were present. On two separate occasions colonmetry was performed and each time, after 200 cc. of fluid had run in, there was a powerful contraction wave with leakage around the tube. Cystometry showed a similar degree of hyperirritability of the bladder (Fig. 4).

Discussion.—The cerebral cortex inhibits the spinal reflex activity of the bladder[2] and apparently of the colon as well. It thereby increases the storage capacity of these hollow viscera. Lesions situated in the cortex or brain stem frequently remove this inhibitory action and result in hypertonicity. Sensation usually remains unaltered.

II. DESTRUCTION OF SPINAL CORD ABOVE SACRAL LEVEL

Case 3.—Rita H., female, age 21. Spina bifida from twelfth thoracic to fourth lumbar vertebra, with infiltrating lipoma.

The patient had had spastic legs and absence of sensation below her eleventh thoracic segment since infancy. In 1933, Dr. W. J. Mixter removed a mass of fatty tissue which compressed the lower end of her spinal cord from the twelfth thoracic to the fourth lumbar vertebra. Little improvement followed, and the patient had just managed to get about with the aid of leg braces and a pair of crutches, but had had the good fortune to have an adequately functioning automatic bladder.

Her colonmetrogram (Fig. 5) shows an unusual hypertonicity of the colon with frequent peristaltic waves and fluctuating alterations of pressure from 40 to 90 cm. Fluoroscopic observation during a barium enema revealed an abnormally large colon with deep peristaltic waves which swept over its transverse and sigmoid loops. The barium was repeatedly forced down against the Foley bag and leaked around it when the balloon was not drawn tightly against the anal sphincter. The patient's only knowledge of filling was brought to her by the increasing spasticity of her legs. It is surprising that an individual with such an unusually hypertonic colon should be very constipated and only able to move her bowels with difficulty once a week.

Case 4.—Stephen C., male, age 18. Epidural abscess in upper thoracic spine (T4 to T6), drained four weeks previously.

In this case an extradural collection of pus had compressed the spinal cord and resulted in a spastic paraplegia with very feeble movements in the left leg and paralysis of the right. Anesthesia was complete in his right lower leg, but some position and pain sensation remained on the left. Colonmetry revealed an increase of tone nearly as intense as that shown in Figure 5. His sensation of filling, which was not destroyed, was most peculiar. He never felt the usual suprapubic cramp-like discomfort, but at 300 cc. noted discomfort in his penis and rectum and at 700 cc. complained of fulness in his chest. Abnormal subjective localization of sensation is not unusual after incomplete spinal injuries and is often seen on distending the bladder, compression of the testicle, and even on cutaneous stimulation.

Discussion.—Unfortunately, we have not yet been able to obtain a colonmetrogram immediately after a transverse injury to the spinal cord in its cervical or thoracic portions. During the stage of "spinal shock" there is a flaccid paralysis of the limbs with abolition of the tendon reflexes. It is also well established that there is a flaccid paralysis of the bladder, since cystometry shows practically no rise in tone or peristaltic contractions, even when a large amount of fluid is run in. During this stage of general reflex depression, patients have abdominal distention with no audible peristalsis, and usually fail to expel an enema or even gas through a rectal tube. Plain roentgenograms reveal large quantities of gas trapped in the small and large intestines. We have colonmetric and cystometric evidence in two patients, secured between two and three weeks after transverse spinal injuries, that the colon recovers its muscular tone more rapidly than the bladder, since in both of these patients the atonic stage persisted in the bladder, whereas the colon was already developing its chronic hypertonic state.

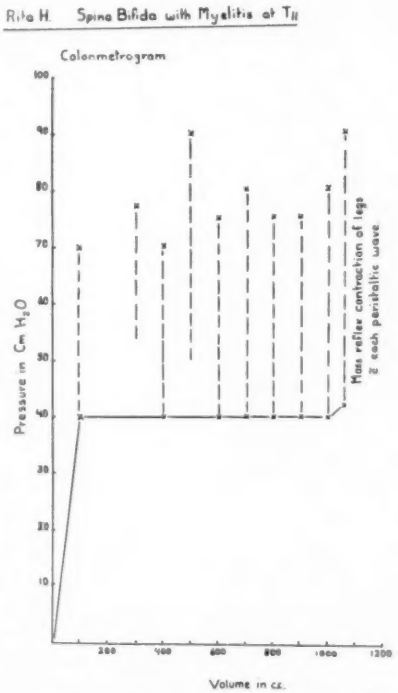
Rita H. Spina Bifida with Myelitis at T11
Colonmetrogram
Pressure in Cm. H2O
Mass reflex contraction of legs
& each peristaltic wave
Volume in cc.

FIG. 5.—Case 3: The "reflex colon" with extreme hypertonia after a transverse spinal lesion at the eleventh thoracic segment.

The remarkable hypertonia which soon develops after high injuries to the spinal cord is well shown in Figure 5. These physiologic changes in the spastic colon have not been adequately described previously, but they closely resemble the condition observed in the bladder by Munro[5] and McLellan[2] after satisfactory treatment and recovery of automatic bladder function. The abnormalities observed in this group of patients are not unlike those in the preceding group with intracranial lesions, except for the fact that patients with spinal injuries have little or no sensation. Both groups may have sudden and imperative necessity to defecate or urinate, or in spite of their hyperactive reflex tone may be definitely constipated, but the patients with spinal injury often do not know when they are soiling themselves.

III. DESTRUCTION OF SACRAL CENTERS IN CORD OR CAUDA EQUINA

Case 5.—Herbert M., male, age 43. Fracture of the twelfth thoracic vertebra one year previously, with compression and injury to cord.

A fall from a scaffolding had resulted in paraplegia, for which a decompressive laminectomy from the eleventh thoracic to the second lumbar vertebra had been performed at another hospital. Thereafter he had recovered to a remarkable degree, so that he could walk without support, although his legs remained somewhat weak and his tendon

reflexes nearly flaccid. He had regained sensation down to the fourth lumbar segment, but remained totally anesthetic over the sacral dermatomes. His bladder, which had been treated by prolonged catheter drainage, was rigid-walled and contracted to 100 cc. maximum capacity. It was totally insensitive and dribbled constantly. His anal sphincter was also paralyzed, but he had not suffered from incontinence.

The colonmetrogram (Fig. 6) shows the characteristic hypotonia and absence of peristaltic waves commonly seen in injury to the sacral centers of the spinal cord or more distal structures. Accurate sensation was gone, although he mentioned a peculiar feeling in his left testicle at a filling of 1,000 cc. and a slight desire to defecate at 2,000 cc. At 2,800 cc. he felt nauseated, but he had no pain or true sense of distention. In spite of these abnormalities the patient did not complain of any difficulty with his bowels.

Case 6.—Emma H., female, age 43. Paralysis of lower sacral nerves after intrathecal alcohol injection.

Two intrathecal injections of 0.8 cc. of absolute alcohol had been performed upon

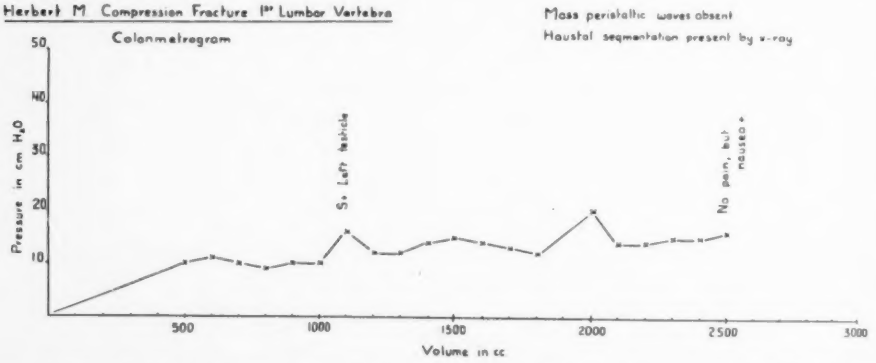

FIG. 6.—Case 5: The atonic colonmetrogram found after injury to the sacral segments of the spinal cord.

this patient six days apart, for the relief of a painful thigh amputation stump. After the second injection she complained of great difficulty in emptying her bladder, with absence of sensation on micturition or defecation. She developed a large urinary residual and had to be placed on tidal drainage. In addition, she noticed that it was difficult to move her bowels without an enema. On neurologic examination, abnormal findings were localized to the structures supplied by the second to fifth sacral nerves. They consisted of a narrow zone of anesthesia around the anus and forward over the perineum to the labia minora, and weakness of her sphincters.

Both her colon and cystometrograms disclosed a state of atonia and flaccid paralysis, with nearly complete loss of sensation (Fig. 7). Peristaltic waves appeared in the colonmetrogram, and the patient noticed an aching sensation above her umbilicus only after distention to 1,700 cc. The bladder was more severely injured and showed no muscular response to stretching.

Discussion.—Destruction of the cauda equina, or of the sacral segments in the spinal cord, produces a severe functional disturbance of the colon as well as the bladder, because the sacral pathways which transmit the contraction reflex are interrupted. Fluoroscopic observations show a loss of peristaltic rush waves, but haustral segmentation remains. Loss of sensation in the lower half of the colon is complete (Fig. 7). It is theoretically possible that the cecum and ascending colon may retain some residual sensation, as this area is supposed to receive its innervation from the splanchnic trunks. Although the

sensation of a full rectum is abolished and the anal sphincter paralyzed, the patient may notice few symptoms beyond mild constipation and soiling when he has diarrhea. Experimental megacolon has been produced in animals by Adamson and Aird[6] by cutting the pelvic nerves, and it would seem as though such a condition were developing in Case 5.

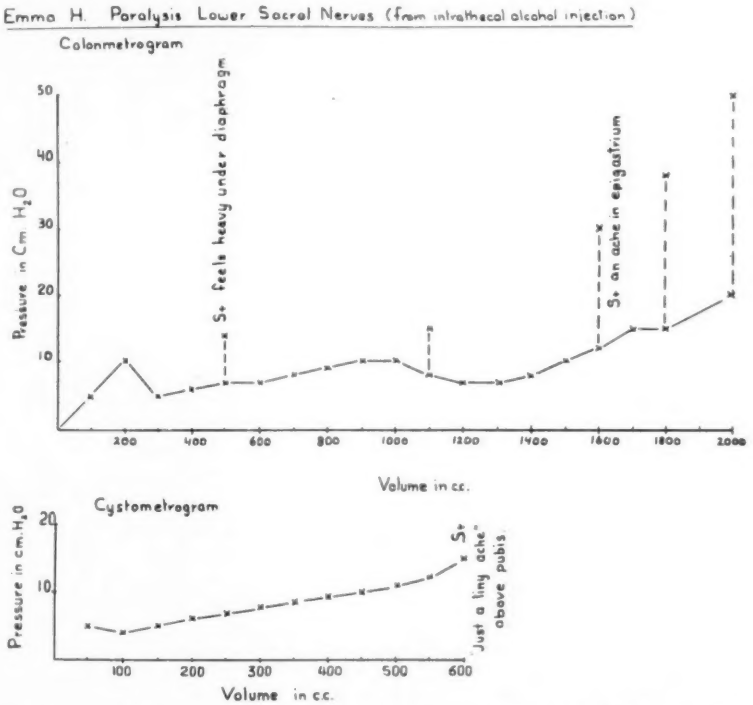

FIG. 7.—Case 6: Hypotonia of colon and atonia of bladder after chemical injury to lower sacral roots in cauda equina.

IV. DESTRUCTION OF LOWER SENSORY NERVE ROOTS AND POSTERIOR COLUMNS

A. In Syphilis of Central Nervous System

A few months before this investigation was begun, a male, age 57, entered the hospital for treatment of long-standing neurosyphilis. He gave a history of increasing constipation and abdominal distention. These symptoms had followed a recent onset of numbness and ataxia in his legs. In a plain abdominal roentgenogram the right half of the colon and lower ileum were seen to be distended with gas. The cecum was huge. In addition, he had an enormously distended bladder. Both the blood Hinton and spinal fluid Wassermann tests were positive. His spinal fluid examination gave normal pressure and dynamics; two lymphocytes; a total protein of 67 mg.; and gold sol. 5555532100. In addition to the typical pupillary findings, ataxia, and loss of deep reflexes, he showed an unusual degree of muscular weakness in his legs with loss of pain and temperature sense. Because the reason for his distention was not recognized and it was felt that rupture of the cecum was imminent, a cecostomy was performed. The cecostomy tube failed to drain and the abdominal distention continued. Signs of bronchopneumonia set in and he died in four days. Autopsy revealed no peritonitis or organic obstruction, but

a thin-walled and enormously dilated colon, moderate distention of the small intestine, and a hypertrophic, chronically dilated bladder. Gross and microscopic examination of the brain and spinal cord established the diagnosis of meningovascular syphilis with recent patchy ischemic lesions of the spinal cord.

The patient died of paralytic ileus. The process involved his entire intestinal tract, but most particularly the cecum and ascending colon. From what we have learned through subsequent investigation the evidence clearly indicates that the acute intestinal paralysis was caused by a syphilitic vascular process with acute degeneration of the sensory and reflex mechanism which mediate defecation.

Colonmetry has since been carried out in three other patients with neurosyphilitic disturbances of defecation:

Case 7.—Frank C., male, age 72. Taboparesis with megacolon.

This patient, the first to be studied by colonmetry, entered the hospital in December, 1938. He was a Cape Verde Island Negro, with much mental deterioration, and an

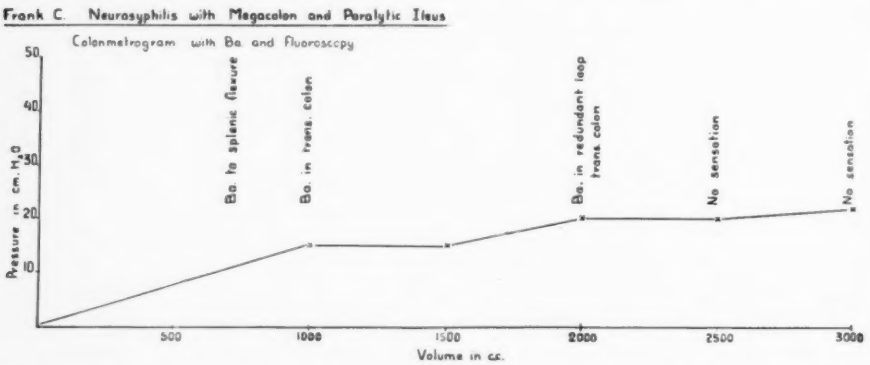

FIG. 8.—Case 7: Extreme atonia and megacolon which may occur in neurosyphilis with involvement of posterior root fibers in sacral cord.

enormously distended abdomen. He said that the illness had begun four months before with pain in the abdomen and increasing constipation. Although vomiting was denied, peristalsis was visible and audible. His pupils were unequal and did not react to light. Position sense in his hands and feet was practically nonexistent and his gait moderately ataxic. His knee jerks were much reduced and ankle jerks absent. Examination of the cerebrospinal fluid was characteristic of general paresis, *i.e.*, protein 45 mg.; eight cells (lymphocytes); Wassermann positive; and gold sol. 5555532110.

Operation for intestinal obstruction was considered, but Dr. G. W. Holmes, who examined the plain roentgenograms, made the diagnosis of megacolon and felt that this could be on a luetic basis. Therapy consisted in colonic irrigations which removed an enormous quantity of fecal material and reduced distention.

A colonmetrogram was performed, using a dilute barium mixture and combining fluoroscopic observation with determination of intracolonic pressure (Fig. 8). At the time of this test his colon was already distended with a large amount of barium which he had been unable to expel after a previous fluoroscopic examination, yet he was able to hold an additional 3,000 cc. without any sense of distention or evidence of peristaltic contractions. A cystometrogram, made a few days later, did not show a similar degree of bladder atonia, although the patient noticed no sensation until over 500 cc. of liquid had been introduced.

Colon- and cystometrograms were made upon two other patients with latent neurosyphilis. Both had positive spinal fluid findings, but failed to show characteristic neurologic signs of the disease. The first case was of interest

from a general surgical viewpoint because constipation and straining at stool had caused a recurrence of his bilateral inguinal herniae after careful repair carried out with fascia lata. Although his cystometrogram was normal, a colonmetrogram disclosed a large bowel of abnormal capacity (3,000 cc.) with low basic tone, absent peristalsis, and markedly diminished sensation. He was able to move his bowels only with extreme difficulty every three to five days and it was felt that this was the cause of his recurrent herniae. The second patient was tested routinely while he was in the hospital for investigation of a urinary residual of from 120 to 400 cc. Cystometry showed a typical tabetic bladder with very poor tone and greatly reduced sensation. His colon had an equally low basic tone and feeble peristalsis, although its sensation was within the normal range.

B. In "Combined System Disease" of Spinal Cord

Case 8.—John D., male, age 69. Pernicious anemia with spastic-ataxic legs and retention of urine from subacute degeneration of posterior and lateral columns of spinal cord.

Unsteadiness in gait had forced the patient to use a cane for three years. Sixteen months before admission he had lost all position-sense in his legs and the ability to walk at all. Difficulty in urination had been present for a week and progressed to complete retention in the last 24 hours; constipation had been troublesome for many years. Blood examination showed: R.B.C. 2,500,000. Hemoglobin 55 per cent. Color index 1.1. Gastric acidity was absent in fasting stomach contents and after histamine. Neurologic examination showed extreme ataxia and spasticity. He had sufficient strength in his legs to stand, but no sensation below the knees and an absence of position and vibration sense from the waist down. In addition his legs were extremely spastic. Figure 9 shows an atonic dilation with absence of peristalsis and abnormal sensation in both the colon and bladder.

Discussion.—In both tabes dorsalis and combined system disease of the spinal cord there is injury to the posterior columns of Goll and Burdach,[7] and in tabes to the sensory root fibers as well. In the tabetic, the spinal stretch reflexes are abolished and reflex contractility of the bladder and colon may be lost. In combined system disease, where there is usually degeneration of both the pyramidal and dorsal tracts, the legs may become spastic. As we have seen, spasticity alone is usually accompanied by hypertonia of the colon and bladder, but whenever there is extensive damage to the posterior roots which carry sensation from the colon and bladder, or of the reflex arc at any point, an atonic dilatation will result. The so-called "tabetic bladder" has long been recognized as a dreaded complication of syphilis of the spinal cord, and a similar condition in severe primary anemias and cachexias is well known. But it is not common knowledge that the degenerative process may also destroy the detrusor mechanism of the colon. We wish, particularly, to bring this to the attention of surgeons, so that it may be recognized that these conditions can produce megacolon, simulate intestinal obstruction, and cause a breaking down of herniae which have been adequately repaired.

In addition to the typical neurogenic disturbances of defecation described above, we have obtained colonmetric evidence of dilatation of the colon with

severe degrees of hypotonia in psychotic depressed patients and others after prolonged constipation from neglect. A flaccid dilatation of the colon has often been observed during fluoroscopic examinations in this group of patients

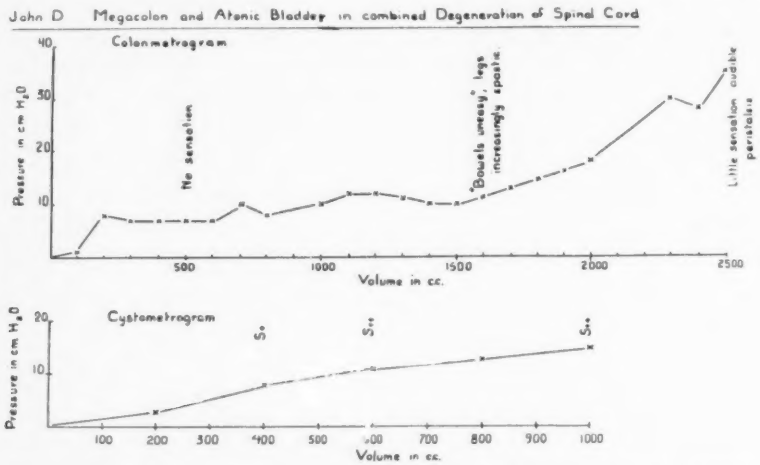

FIG. 9.—Case 8: Flaccid paralysis of colon and bladder with dilatation seen in a patient with combined system disease.

by Dr. J. R. Lingley,[8] who has made a special study of this problem. The condition may be classified as "acquired megacolon" and is not due primarily to lesions of the descending pathways or of the spinal reflex arc.

TABLE I

NEUROGENIC DISTURBANCES OF THE COLON

Case No.	Pathologic Lesion	Uninhibited Colon	Reflex Colon	Autonomous Colon	Atonic Colon	Peristaltic Waves	Sensation	Colon Capacity
1	Parasellar cyst, epidermoid	+				Increased	Normal	Greatly decreased
2	Left frontotemporal glioma	+				Increased	?	Greatly decreased
3	Spina bifida, with transverse myelitis to T_{11}		+			Increased	o	Increased
4	Epidural abscess, with incomplete destruction of cord T_4–T_6		+			Increased	Present but abnormal	Slightly decreased
5	Compression fracture of T_{12} vertebra, with recovery down to lower lumbar segments			+		Absent	o	Greatly increased
6	Chemical destruction of sacral nerves			+		Reduced	Much reduced	Normal
7	Taboparesis, with paralytic ileus				+	Absent	o	Megacolon
8	Combined degeneration of spinal cord				+	Absent	o	Greatly increased

General Discussion.—Injuries to the brain, spinal cord, and sacral parasympathetic nerves may be followed by serious disturbances in defecation. Similar neurogenic disturbances in vesical function have been recognized for years and referred to, both ungrammatically and unphysiologically, as "cord-

bladder." Through the physiologic investigations of Elliott,[9] and the more recent neurologic and clinical studies of Denny-Brown and Robertson,[10] Langworthy and Kolb,[11] Munro[5] and McLellan,[2] it has been established that the bladder reacts reflexly to distention and stretching of its walls. Since this response of smooth muscle is mediated by a reflex arc through the spinal cord, it is affected by a neurologic lesion in a manner quite analogous to that observed in skeletal muscle. It is the purpose of this communication to show that a similar mechanism governs the activity of the colon and that injury to its cortical centers, descending pathways, or reflex arcs can be fitted into an exact neurologic classification. By observing the reaction of the colon to distention, we can determine whether its muscular tone is normal, increased, decreased, or absent; whether the upper or lower motor neuron is functioning abnormally; and whether the lesion involves the sensory or the motor portion of the reflex arc.

Disease or injury of the brain and descending tracts of spinal cord removes cerebral control over the reflex peristaltic contractions which sweep the fecal contents down the colon and pack it into the rectum. In the baby, and in some adult idiots, cerebral voluntary control of micturition and defecation is not developed. Urine and feces are ejected at irregular intervals in response to a stretch reflex. With the gradual development of cortical function, a cerebral control is established over these spinal reflexes. Its elimination results in increased reflex contractions in the smooth muscle which lines the hollow viscera. Injury to the brain or to the tracts in the spinal cord produces an identical increase in the tone of the colon and bladder. After the initial flaccid paralysis has been replaced by the permanent spastic state, a reversion to the infantile condition is common, with precipitate evacuation of urine and, to a lesser extent, feces. In spinal lesions sensation is lost in addition to cortical control. The resulting disturbances are shown in Figures 3 to 5.

Elliott[9] found that destruction of the spinal cord at progressively lower levels did not destroy reflex evacuation of the bladder until the second, third, and fourth sacral segments were removed. Destruction of these segments, which give rise to the parasympathetic motor as well as the sensory fibers to the bladder, abolishes reflex activity. This also appears to be the case with the colon in man. It would seem, furthermore, that the sacral nerves constitute the only motor and sensory pathway to the colon. We have made colonmetric studies upon two patients before and after extensive lumbar ganglionectomies, and on two others with bilateral lumbar ganglionectomy plus splanchnicectomy, and have been unable to detect any significant change either in the motor response to filling or in sensation.* Figures 6 and 7 illustrate the reduction in tone and peristaltic contractions which, together with a loss of the normal sensation of distention, characterizes destruction of the spinal reflex arc, *i.e.*, cells in the sacral segments of the cord or of their axones

* The conclusion that the thoracolumbar sympathetic rami carry no important sensorimotor fibers to the bladder has already been reached by Munro[5] and McLellan.[2]

in the cauda equina and pelvic nerves. Lesions of this sort cause a much greater disturbance in the excretory processes than those which affect the tracts and brain.

An even greater disturbance of the bladder and colon results from destruction of the afferent fibers in the posterior sacral roots or in the sacral portion of the spinal cord. The bladder disturbances in tabes dorsalis and combined system diseases have been commonly recognized, but this has not been the case with the colon. Disturbances of the nervous mechanism that evacuates the colon may be very severe and lead to fatal ileus or simulate intestinal obstruction. Because the paralysis of the colon is of the flaccid type, colostomy is more likely to do harm than good. These patients may also develop striking degrees of megacolon (Fig. 8), but there is no reason to suppose that the dilated, atonic bowel can be improved by sympathectomy. The only logical way to handle these conditions is by early, adequate treatment. The filling curves of the bladder and colon should be determined when the patient with neurosyphilis or pernicious anemia first complains of sensory disturbances, because medical treatment of these diseases can prevent their neurologic complications far more effectively than it can correct them in their advanced stages.

A final point, which we wish to emphasize, is that the neurogenic mechanism is not necessarily upset to the same degree in both bladder and colon. For example, the filling curves in Case 6 (Fig. 7) illustrate a distinctly greater loss of tone and reflex activity in the bladder than in the colon. On the other hand, in Case 7, and in the next patient with neurosyphilis described above, there was much less paralysis and sensory loss in the bladder than in the colon. While the reflex arcs to the bladder and colon follow a closely similar course, it is evident that they are not exactly similar.

CLASSIFICATION OF NEUROGENIC DISTURBANCES OF THE COLON

Munro[5] has proposed a valuable classification of bladder disturbances which result from neurologic lesions. This has been expanded in McLellan's[2] recent monograph on the "neurogenic bladder." The same classification can be applied with equal satisfaction to neurogenic disturbances of the colon, and is reproduced, herewith, in the form given by McLellan with necessary minor adaptations to the colon. This classification should be compared with the data given in Table 1.

GROUP I: THE UNINHIBITED COLON (FIGS. 3 AND 4)

Resulting from lack or loss of cerebral inhibition, either from failure of development, cortical disease, or subtotal destruction of the spinal cord pathways—defecation is imperative, but voluntary. Sensory pathways are intact.

GROUP II: THE REFLEX COLON (FIG. 5)

Resulting from widespread injury of the controlling mechanisms from disease or injury of the brain (sensory as well as motor cortex or brain stem),

or from destruction of the cord (above the sacral segments)—defecation is purely reflex, but often less imperative or precipitate than the evacuation of urine. Sensation is abolished.

GROUP III: THE AUTONOMOUS COLON (FIGS. 6 AND 7)

Resulting from nuclear or infranuclear lesions of the sacral cord, cauda equina, or sacral plexus with interruption of both afferent and efferent fibers of the spinal reflex arc. Only segmental peristalsis (haustral markings) remains and is presumably mediated by the intrinsic plexuses of Meisner and Auerbach. Emptying of the colon is impaired, but less so than the bladder. Mild degrees of megacolon may result. Sensation is abolished.

GROUP IV: THE ATONIC COLON (FIGS. 8 AND 9)

Resulting from lesions of the pelvic parasympathetic nerves, or posterior sacral roots and columns with interruption of the afferent fibers of the reflex arc. There is a profound disturbance of normal voluntary and reflex evacuation, which may be as severe in the colon as in the bladder. Extreme degrees of megacolon may result. Sensation is abolished.

SUMMARY AND CONCLUSIONS

(1) The colonmetrogram is the filling curve obtained by slowly distending the large intestine with warm water. The resultant graph, in which the intracolonic pressure is plotted against the volume of liquid introduced, closely resembles the cystometrogram. A normal colon can accommodate itself to a volume roughly four times greater than the bladder.

(2) Colonmetry gives a picture of the motor activity and sensation of the colon as a whole. It fails to bring out circumscribed disturbances in the rectum, sigmoid, or upper portions of the large bowel. This is not a serious objection in nerve lesions, because neurogenic disturbances characteristically affect the entire length of the colon.

(3) The longitudinal and circular smooth muscle of the large intestine reacts to increased filling by periodic attempts to evacuate. This is illustrated in the colonmetrogram by intermittent rises in pressure and in the fluoroscopic examination by peristaltic rush waves which sweep the fecal contents down into the rectum.

(4) The peristaltic contractions are a form of "stretch-reflex." The afferent and efferent arcs of this spinal reflex run over the parasympathetic sacral rami; the second, third, and fourth sacral roots in the cauda equina; and the corresponding segments in the lower end of the spinal cord.

(5) The normal patient becomes aware of a sensation of filling in his colon or bladder at a pressure between 20 and 30 cm. of water. At 40 to 50 cm. there is a real urge to defecate or urinate, and at higher pressures distinct low abdominal pain.

(6) Lesions to the brain, spinal cord, and sacral nerves produce characteristic disturbances in the physiologic mechanism of evacuation, which are

common to both colon and bladder. These are analogous to alterations in the knee jerk and other tendon jerks, which are dependent upon the stretch-reflex of skeletal muscle.

(7) The colonmetrogram shows a hypertonic response to filling with lesions of the motor fibers in the brain or in the descending spinal tracts (spastic paralysis); and an atonic bowel when the lesion is situated in the sacral segments of the cord, cauda equina, or pelvic plexuses (flaccid paralysis). In addition, much depends on the degree of sensory loss, the severest grades of paralysis being found in patients with degenerative disease of the sensory fibers in the sacral cord.

(8) These changes are illustrated by a series of colonmetrograms obtained from patients with lesions at various levels of the nervous system.

(9) It is shown that the same neurologic classification that has been adopted for injuries of bladder innervation can be applied to the colon. The colonmetrogram, like the cystometrogram, is a valuable aid for differential diagnosis of the level of the nervous system which is destroyed by injury or disease.

(10) Neurologic disturbances of defecation, which are of importance to the general surgeon, can best be evaluated by colonmetry. These comprise cases of acute ileus seen after injury to the spinal cord and in rarer instances of spinal neurosyphilis. A variety of megacolon, as well as of atonic paralysis of the bladder, is not uncommon in patients with neurosyphilis or combined system disease. These patients are forced to strain so hard to move their bowels that herniae may be produced. In addition, the patient with spastic or flaccid paraplegia often complains of difficulty in evacuating his bowels as well as his bladder.

We wish to express our thanks to the members of the Roentgenologic Department of the Massachusetts General Hospital for their assistance in studying pressure-volume reactions of the colon by direct fluoroscopic observations in the course of colonmetry.

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DISCUSSION.—DR. PETER HEINBECKER (St. Louis, Mo.): I wish to express our gratitude to Doctor White for this presentation in which he has depicted for us the development of colonmetrography. I feel that this method, especially when combined with anesthesia at the proper level, should help us to decide whether or not interference with the sympathetic nerve supply would do good in many cases of functional disturbance of the bowel.

DR. JAMES C. WHITE (Boston, Mass., closing): I might take just one moment to say that I think the next stage in this work is going to be to see what happens after different operative lesions. I know that after a satisfactory cordotomy the bladder sensation is little changed and the bladder reflexes are preserved. We have been interested in doing colonmetrograms as well as cystometrograms after injury to the sympathetic pathways alone. We have found that the colonmetrogram in a patient after bilateral lumbar ganglionectomy for Raynaud's disease or in a patient in whom the upper lumbar ganglia as well as both splanchnic nerves have been removed for hypertension, shows no change in the motor responses of the colon or bladder. We have not been able to detect any sensory changes either. All of these tests have been made upon normal colons, and it looks as though all sensation, as well as all motor control, must come over these second, third, and fourth pairs of sacral parasympathetic rami. That is the conclusion reached by Munro, McLellan, and Denny-Brown and Robertson, who did such careful work on the bladder, and by the last two investigators for the rectal innervation as well. We wonder what happens in children with Hirschsprung's disease, who we know react so well to removal of the sympathetic nerve supply. To date, no opportunity has presented itself to test the motor and sensory responses in a case of megacolon before and after sympathectomy.

THE EARLY SYMPTOMS AND TREATMENT OF NASOPHARYNGEAL TUMORS*

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IT IS NOT an uncommon experience for the neurologic surgeon to be consulted by a patient who has suddenly developed unilateral paralysis of the extra-ocular muscles, pain or numbness in the areas of distribution of the trigeminal nerve, and even signs of destruction of the cranial nerves which lie in the posterior cranial fossa, with little or no evidence of an increase in intracranial pressure.

Such symptoms should suggest several possible intracranial lesions, not the least of which is an extension of a malignant tumor of the nasopharynx, accessory nasal sinuses, or middle ear cavity. We have recently had occasion to study the histories of 15 such patients with malignant neoplasms of the upper respiratory tract. Nine of these cases were from the files of the Cushing Tumor Registry, and the other six patients were referred to us for neurologic consultation and treatment. We have been so impressed by the uniformity of both the early and late symptoms in these patients, as well as by the fact that they frequently have not had an adequate early examination of their pharynx, nose, and ears, and have not had a complete history recorded, that we believe that a restatement of the early symptoms is particularly important.

Gordon New,[1] in 1922, emphasized the fact that the effects of the regional metastases of nasopharyngeal malignancies, such as facial pain and diplopia, and not the effects of the primary lesion, may bring the patient to the physician. It was his plea, then, that the *early* symptoms of such tumors be recognized for their full value. It is true that the signs of metastases may develop rapidly, but in the 15 cases which we have studied this never occurred in the absence of unmistakable signs of the primary tumor, which should have been provocative of a careful examination, if not an actual diagnosis.

A patient with a malignant tumor of the nasopharynx which is still a local growth may complain of a stuffiness or feeling of fullness in the nose, and frequently there is a thin, watery nasal discharge, or even mucopus. Slight or massive spontaneous nasal hemorrhages occur from time to time. Anosmia and fetor may be present. A fulness in the ear, perhaps with tinnitus, will be relieved only temporarily by eustachian insufflation. There may be a complaint of moderate earache, with pain radiating down the wall of the pharynx

* Presented by title before the American Surgical Association, St. Louis, Mo., May 1, 2, 3, 1940.

into the neck. Deafness may cause the patient to seek an examination of his ears, and one or both drums will be found to be dull, sclerotic, and retracted. Not infrequently a seropurulent discharge appears suddenly from the middle ear and drains persistently from an opening in the drum. Very frequently there is unilateral cervical adenopathy and occasionally it is bilateral. The patient may complain of a feeling of thickness in the region of the soft palate, swallowing becomes difficult, and the speech becomes nasal in quality. Almost always there is either a localized headache or pain in the trigeminal area of the face; sometimes the patient locates the pain only vaguely, deep within the face.

Any patient with such a train of symptoms obviously deserves a thorough examination by someone competent to recognize even a small lesion which may lie in the pharyngeal or nasal cavities. Nasal polypoid masses are not always "simple polypi"; a "hyperplastic" nasal, or pharyngeal mucous membrane requires more than casual observations; nasal discharge or epistaxis never occurs without good cause; "thickening" of "nodules" in the vault of the pharynx may not be "lymphoid hyperplasia"; sinus membranes may be more than "cystically degenerated" or "chronically thickened"; and facial pain can be caused by disease other than infected teeth or tonsils. In short, a painstaking examination of the ears, sinuses, nasal passages, and nasopharynx must be accomplished, and it is a rare patient indeed who cannot be so examined, either by direct view with a nasopharyngoscope or indirectly with a mirror. Any mass, thus discovered, should be biopsied and the patient held under observation until a diagnosis has been made. It must be emphasized, also, that the biopsy should not be too superficial, for some carcinomata of the nasopharynx may, especially in their early stages, be submucosal, and a shallow biopsy will reveal only lymphoid infiltration. Roentgenographic evidence of an early malignancy in the epipharynx, nose, or ear is usually lacking.

If a malignant tumor is discovered, deep roentgenotherapy or radium treatment may be begun at once, and while the growth is still local the prognosis is not too unfavorable. Examination having failed to disclose a growth, or, as is more often the case, no examination having been made, the patient next appears with unmistakable signs of intracranial spread, and the eventual outlook is then generally unfavorable. A unilateral primary lesion often presents early only unilateral symptoms, but the signs of intracranial extension are frequently bilateral or even contralateral. The spreading tumor, extending along the floor of the cranium, may or may not produce blindness, but such blindness is due to direct pressure and invasion of the optic nerve, and is not the result of postedema atrophy. The third, fourth, and sixth nerves are usually involved early in the spread of the growing mass, so that diplopia of increasing severity becomes a source of great concern to the patient. Complete ptosis and ophthalmoplegia are common in the later stages. Pain in the area of supply of any one, or all, of the branches of the trigeminal nerve frequently appears and a full blown Gradenigo syndrome may develop, which, with a discharging ear, will sometimes be the source of confusion in diagnosis. The

facial pain is usually not paroxysmal but is frequently felt as a deep-seated, poorly localized distress, and not uncommonly an area of hypesthesia or actual sensory loss will be found on examination. The occasional patient develops a complete facial paralysis, and tinnitus or vertigo is a usual and early sign of intracranial spread to the posterior cranial fossa. Deafness was complete in three of our cases. Palatal weakness with the resultant changes in speech and deglutition, together with nausea and vomiting, speaks for an expansion of the tumor along the brain stem. Again, roentgenograms, more frequently than not, will show no bony changes, and, indeed, at this time they are hardly needed, for with such positive evidence of the location of a spreading tumor, the diagnosis becomes self-evident. The gross appearance of the mass in the nasopharynx at this late stage is so characteristic that biopsy becomes merely a confirmatory procedure.

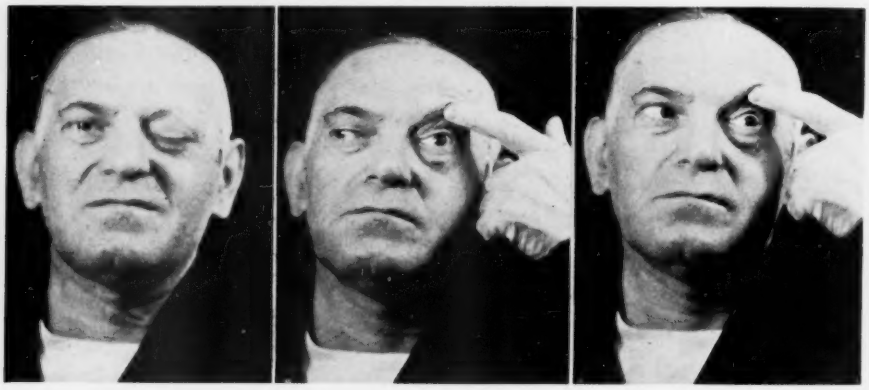

FIG. 1. FIG. 2. FIG. 3.

FIG. 1.—Case 1: One week after operation. Showing the complete ptosis of the left upper lid which had been present for six weeks.
FIG. 2.—The same patient, looking to the right, showing the ophthalmoplegia on the left.
FIG. 3.—The same patient, looking to the left. There was no motion in the left eye upon looking in any direction. The pupil was fixed in moderate dilatation, and the eye was completely blind.

Two typical cases which have been under our direct observation and care are reviewed briefly:

Case 1.—L. K., white, male, age 45, had suffered from a left-sided headache for seven weeks, localized vaguely behind the left eye, and for five weeks had noted a progressive ptosis and dimming of vision of the left eye. Upon his first admission to the hospital there was a complete left ptosis, left ophthalmoplegia, loss of all vision in the left eye, dilation and fixation of the left pupil, and loss of sensation to pain and light touch over the left cheek (Figs. 1, 2, and 3). He had had a "stuffy" left nostril for some time without any other sign of respiratory infection. He had lost 15 pounds in weight. There was no loss of smell, hearing, taste, or the ability to move either side of the face, to swallow, or to speak normally. Casual examination of the nose and throat revealed nothing, but upon careful inspection of the superior meatus on the left a gray, firm, cartilage-like mass was seen, obscuring all view of the ethmoid area. It was painless and bled but little on being touched. Roentgenograms revealed a beginning erosion of the floor of the left middle cranial fossa. A subtemporal exploratory operation, under local anesthesia, brought into view a tumor mass lying anteriorly, under the wing of the sphenoid bone, deep within the middle cranial fossa. Tissue from this tumor and from

that of the nose revealed a myxoid type of sarcoma with frequent islands of cartilage and few mitotic figures (Figs. 4 and 5).

The patient had several attacks of nosebleed while in the hospital but he made a prompt recovery from his operation. Deep roentgenotherapy was started at once, following which he felt somewhat improved, but though there was some improvement in the ptosis on the left, there was progressive loss of vision in the right eye, so that he was totally blind in both eyes two months after he was first seen. At no time was there any papilledema. Four months after his operation, he was admitted through the emergency ward following a massive and uncontrollable nasal hemorrhage. The nasal tumor had become a huge, ulcerated mass, completely filling the left side of the nose and nasopharynx. There was at that time a complete recovery of the left ptosis, and perfectly normal movement of the right eyeball was still present. There was no cervical

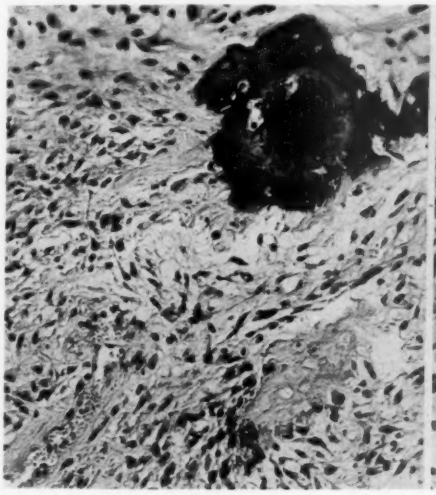

FIG. 4.

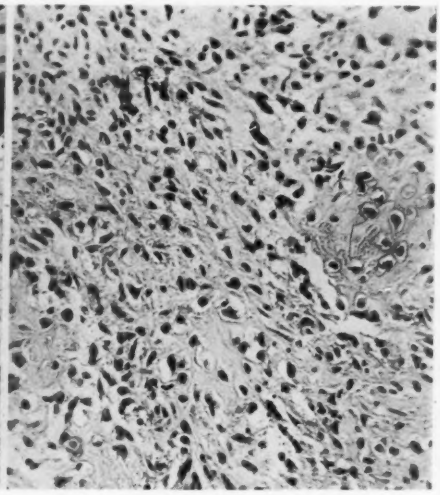

FIG. 5.

FIG. 4.—Case 1: This photomicrograph (×130) is from tissue removed for biopsy from the nose, and it shows discrete islands of both adult and embryonic cartilage. The main mass of tissue is made up of large stellate- or spindle-shaped cells which are not closely packed and which lie in a moderately vascular, somewhat vascuolated, collagenous, intercellular groundwork. Mitoses are not particularly abundant. There is a large element of fibrocytes. *Pathologic Diagnosis:* Spindle cell myxosarcoma with cartilage formation, of low malignancy.

FIG. 5.—Case 1: This photomicrograph (×130) is from tissue removed at operation from the middle cranial fossa, and it answers the same approximate description as does that of Figure 4. There is no adult cartilage in this intracranial tumor, however, and the young cartilage, which is quite abundant and makes up approximately one-fifth of the tumor, is a much more prominent feature than it is in the primary or nasal lesion.

adenopathy. In his terminal stage, his intracranial symptoms consisted of bilateral complete blindness, paralysis of the left third, fourth, and sixth nerves, loss of sensation in the area of supply of the left maxillary nerve, and severe generalized headache. He failed rapidly and died five days after his second admission. Permission for autopsy was refused.

COMMENT.—This patient illustrates the fact that prodromal nasopharyngeal symptoms may be quite meager and precede for a short time only, the signs of intracranial extension. However, had this man had a thorough examination of his nose when he first began to complain of headache, nasal blockage, and drooping of the left lid, the tumor no doubt could have been identified. The intracranial mass must have remained localized to the middle

fossa, probably extending backward from the original tumor through the posterior ethmoid and sphenoid area, and though the mass was demonstrated at operation to be of a considerable size, fundus examination at no time during the four-month period showed any swelling of the optic disks. It is doubtful if any form of either surgical or radiation therapy could have controlled this tumor.

A more encouraging outcome resulted in another patient who gave a typical history and clinical findings of a nasopharyngeal tumor with intracranial extension:

Case 2.—R. C., white, male, age 30, was admitted for neurologic study because of a diminution of hearing and a sensation that the left ear was plugged shut for five and one-half weeks; right-sided periorbital pain for five weeks; diplopia on looking to the right for three weeks; numbness of the skin under the right eye for two weeks, and difficulty in swallowing for two weeks. He had had a nasal discharge of mucopus for several weeks. He was found to have a widened left palpebral fissure, a complete right rectus paralysis, nystagmus on looking to the left, anesthesia of the right maxillary area, diminution of the right corneal reflex, deafness in the left ear, a paralysis of the left side of the soft palate, and a voice of nasal quality. There was no complaint of headache. The pupillary reflexes were intact, there were no changes in the retinae, no papilledema, and no loss in the visual fields. Examination of the ears revealed bilaterally sclerotic tympanic membranes with an old perforation on the right. In the vault of the nasopharynx, obstructing the orifice of the left eustachian tube, was a mulberry-like mass of nodular tissue the size of a large olive, and extending from it across the roof and to the right side of the nasopharynx was an apron-like sheet of the same tissue. Large vessels were seen in the mass. A biopsy of the tumor, which was made with great caution because of its vascularity, was returned with the diagnosis of "dense lymphoid infiltration with chronic inflammation." Because of the gross appearance of the lesion so typical of carcinoma, and because of the undeniable signs of intracranial extension, the patient was immediately started upon a course of radium treatment. For the next six months he received, as an ambulatory patient, 4,000 mg. hrs. of radium over the left nasopharyngeal area, 4,000 mg. hrs. over the right nasopharyngeal area, 248,000 mg. hrs. over the right temporal area, and 46,000 mg. hrs. anteriorly over the nose, all in the form of external packs. Three and one-half months after the beginning of this treatment, only a small pea-sized nubbin of sclerotic tumor tissue remained in the vault just to the left of the midline, and most of his neurologic symptoms had disappeared. Now, three years following his last treatment, he is in perfect health; has not a single vestige of his former intracranial complications; and the mucosa of his epipharynx is smooth, thin, and moderately atrophic.

COMMENT.—This man undoubtedly had a visible nasopharyngeal tumor before he developed an intracranial extension, for the complaints of deafness, nasal discharge, and a feeling of fulness in the left ear were logical ones, considering the site of the main tumor mass. The case illustrates the fact that the most striking neurologic sign, in this case paralysis of the right lateral rectus, may be contralateral to the primary lesion, but that, as in Case 1, the intracranial symptoms eventually become bilateral. We are positive, from the gross appearance of the tumor, the intracranial symptoms, and the response to radium treatment, that this tumor was a carcinoma; and we are more than ever impressed that a biopsy, to be of any value at all, must be deep and furnish an adequate amount of tissue. It is quite conceivable that a lymphoid reaction had occurred over the surface of this tumor, and from this

example it is apparent that when this is true this superficial layer of tissue must be passed through before the actual tumor tissue can be reached. We consider this case a complete cure to date, and would compare it to a similar case reported by Sargnon and his associates.[2]

This paper is not intended to be a histopathologic discussion, but mention should be made of the types of tumors in this series, of the probable method of their extension into the cranial cavity, and of the confusion of pathologic terms used in the description of malignancies of the upper respiratory tract. The patients in our series varied in age from 13 to 78 years. Eleven were males,

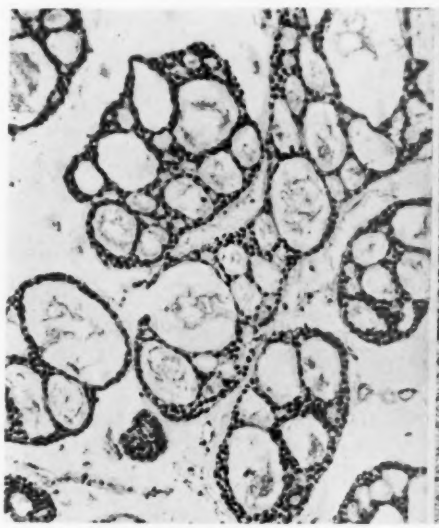

FIG. 6.

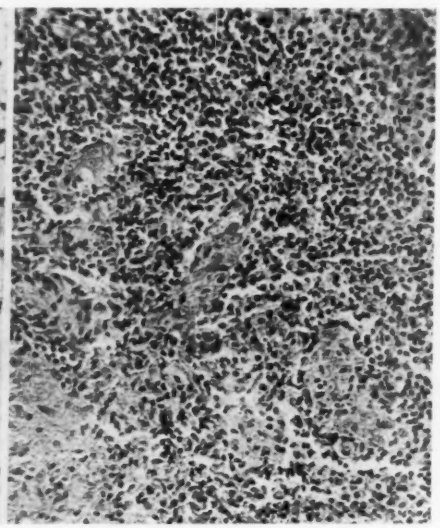

FIG. 7.

FIG. 6.—Case S. C.: Because of severe and intractable pain in the entire area of distribution of the right trigeminal nerve, due to a carcinoma of the right maxillary sinus, a section of the posterior root of the trigeminal nerve was undertaken. This photomicrograph (×130), is from an intracranial extension of the antral tumor, the secondary tumor mass filling the inner portion of the right middle cranial fossa. The tissue was white, soft, and gelatinous in consistency when it was removed from the area of the gasserian ganglion. It is composed of small, gland-like structures, resembling acini or alveoli. Occasionally these formations are solid, but usually their walls are but two or three cell-layers thick, and they are filled with a colloidal-like substance which stains poorly. The cells are flattened and cuboidal, contain a darkly-staining nucleus and scant cytoplasm, and show only an occasional mitotic figure. *Pathologic Diagnosis:* Adenocarcinoma.

FIG. 7.—Case W. H.: This photomicrograph (×175) is taken from biopsy material from a nasopharyngeal tumor in a patient who had advanced signs of intracranial extension. There are fairly discrete masses of large, oval, squamous-like cells, with pale, centrally placed nuclei and light staining cytoplasm. Many of these cells show mitotic figures. There is no keratinization. There is a marked lymphocytic infiltration, with some fibrocytes. This type of tumor is, therefore, frequently called lymphocarcinoma. We prefer the simpler term squamous cell carcinoma.

and four females. In 12 patients the tumors were carcinomata, two were sarcomata, and one was a "lymphoma." The primary tumor was in the nasopharynx in seven cases; ear, two cases; nose, three cases; sinuses, three cases (two antrum, one ethmoid). Every case showed far advanced signs of intracranial spread, and several of the patients experienced their first otolaryngologic examination only after coming under neurologic observation!

The method of extension of these tumors has been believed to be by one of three pathways: (1) By the lymphatics; (2) by the blood vessels (veins);

and (3) by direct tissue extension. Certainly lymphatic metastasis can and does occur into the cervical lymph nodes, but the most likely and most demonstrable pathway of intracranial spread is that of direct invasion. The many foramina at the base of the skull, the patent eustachian tubes, the thin-walled sinuses (sphenoid, ethmoid), and the occasional persistent Rathke pouch, all invite direct extension of a malignant, expanding mass in their close vicinity. Certainly, the orderly progression of intracranial symptoms indicates a spread of the tumor in this manner, and besides, there are no intracranial lymphatics.

The matter of terminology has reached a stage of such an admixture of names for these tumors that one author scarcely knows what another means when a tumor is classified according to some special type. At present "lymphoid" tumors are called lympho-endothelioma, lymphoma, lymphoblastoma, lymphosarcoma, and lymphocarcinoma. Sarcomata are classified as round cell, spindle cell, giant cell, melanomyxo-, chondro-, and fibrosarcoma, according to their predominating microscopic characteristic. Carcinomata lead the list for variety, probably because they are the most common tumor of a malignant nature to be found in the nose and nasopharynx. They are called squamous cell, basal cell, transitional cell, anaplastic, keratinizing, nonkeratinizing, scirrhous, adenomatous, or cylindromatous, with little regard for a histogenetic classification on the embryologic cell type. Hauser and Brownell[3] believe they show "that all epithelial neoplasms arising from the membranes of the nasopharynx are medullary, squamous cell carcinomata, and that it is not necessary to employ such terms as lympho-epithelioma and transitional cell carcinoma." Furstenberg[4] agrees that the commonest lesion is the squamous cell carcinoma. Salinger and Pearlman,[5] in an extensive histopathologic study, would classify nasopharyngeal malignant tumors as carcinoma, sarcoma, and endothelioma. They, too, recognize the confusion in present day terminology, but they feel justified in using the terms "anaplastic" and "transitional cell" carcinoma.

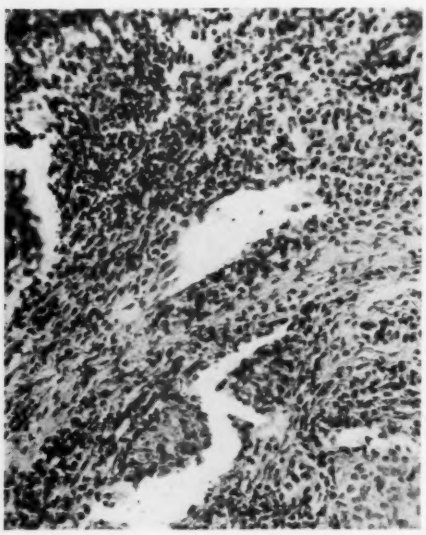

FIG. 8.—Case I. P.: A biopsy of this tumor mass from the fossa of Rosenmüller revealed a vascular tumor of mixed cell type. Large, clear, squamous-like cells occur in collections and are also mixed throughout the remainder of the tissue which is made up of lymphocytes and dense fibrous areas where the cells are almost all adult fibrocytes. There is no keratin formation. Mitoses are fairly common and may be seen in this photomicrograph (×175). The tumor is of uneven structure, some areas being of low cellularity, others densely packed. The patient died of an intracranial extension of the tumor. *Pathologic Diagnosis:* Squamous cell carcinoma.

In any event, squamous cell carcinomata are apparently the most frequent malignant tumors of the epipharynx, nose, and middle ear (Figs. 6, 7, and 8).

In the pharynx, they are slow-growing, firm, sessile, vascular, and appear either as a local, elevated nodule or as a thinner, more sheet-like mass which may cover several square centimeters of the vault. In the nose, they may appear to be hard, rubbery, and not at all vascular, or they may appear to be a soft, irregular ulcerated mass which bleeds on the slightest provocation. In one elderly patient the nasal carcinoma was a pale, flat, watery mass which resembled very closely a sessile polyp. Carcinomata of the middle ear cavity, evaginating through a rupture in the tympanic membrane, may, at first, be mistaken for a polyp, and in one of our cases several such "polypi" were removed in succession until it occurred to the examiner that a biopsy might explain the reason for their regrowth. It did; the "polypi" were carcinoma.

When a primary lesion of the nose, ear, or pharynx is not seen or suspected, but the patient is suffering from progressive symptoms of some sort of basilar cranial lesion, the problem becomes first of all one of differential diagnosis. Paratrigeminal lesions, most commonly meningiomata or aneurysms, such as have recently been described by us,[6] will come first to mind, and the signs of intracranial involvement may be so localized to the middle fossa as to lead to operation. Chordomata, basilar meningiomata, acoustic neurinomata, and aneurysms must be excluded until the primary tumor has been discovered, but in most cases their exclusion will not be a difficult task.

We believe, after a study of this group of cases, and of some of those reported elsewhere, that it is the responsibility of every physician treating diseases of the ear, nose, and throat to be alert to the possible presence of malignant tumors in his field of examination; to look with suspicion upon the patient who complains of vague or incomplete symptoms of the upper respiratory tract; that it is usually evidence of carelessness on some examiner's part at some time during the patient's history, if the patient arrives in the hands of the neurologic surgeon with signs of intracranial extension from a nasopharyngeal tumor which is only then seen for the first time. It is not denied that such lesions present a challenge to accurate early diagnosis, but it is apparently true that frequently the early diagnostic studies are inadequate and desultory.

One cannot review this subject and emerge completely optimistic over the general prognosis, yet we would not agree with Furstenberg[4] that "treatment is exceedingly futile and the prognosis hopelessly discouraging." An early diagnosis with the early institution of radium or deep roentgenotherapy, the histologic characteristics of the tumor having been established, seems to offer the best source of a hope for control of the tumor. It is doubtful if surgery ever accomplishes very much in the treatment of a nasopharyngeal malignancy; the location and tendency to direct intracranial spread preclude the effectiveness of any type of operation which has so far been attempted.

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TRANSTHORACIC BRONCHOTOMY FOR REMOVAL OF BENIGN TUMORS OF THE BRONCHI*

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BRONCHOTOMY, in its narrower sense of incision into a bronchus, apparently dates from 1900, when Gluck proposed the operation for low tracheal stenosis; it had the object of permitting retrograde respiration through a large bronchial fistula. The operation seems to have been discussed and written about more than it was actually carried out. Sauerbruch mentions having performed it once; most other texts on thoracic surgery fail to mention it. The bronchotomies of older authors, from Bonetus down, reviewed by Gross in his treatise on foreign bodies in the air passages, include operative openings into the larynx and trachea, but not the bronchi. The lower bronchi, however, have been entered, *via* a posterior mediastinal route, with the object of extracting foreign bodies. Schwartz, in Quénu's Clinic, worked out such a procedure which was carried out successfully by Duncan, Schiasso, *et al.*: Danielson mentions three transpleural bronchotomies. The establishment of a large bronchial fistula may, occasionally, be indicated for incurable low tracheal stenosis; modern bronchoscopic methods have superseded bronchotomy for removal of foreign bodies.

Formal bronchotomy may have a place, however, in the treatment of benign bronchial tumors. Bigger,[1] in 1935, reported an operation performed upon a boy for a tumor of the left main bronchus. The bronchus was incised and the tumor removed; one week later the chest was reopened and the left lung removed. The course was complicated by a purulent pericarditis, to which the patient succumbed. Many pedunculated benign tumors, especially adenomata, may be removed bronchoscopically; they may be avulsed with a forceps or snare and their pedicles may be coagulated or cauterized. Some tumors, however, cannot be treated satisfactorily by endoscopic methods, especially those with pedicles originating in the upper lobe bronchus and sessile tumors with a broad base. Such tumors may be reached, and the possibility of their removal more accurately estimated through an incision into the bronchus than through a bronchoscope. Bronchotomy may even be justifiable for some more accessible bronchial growths. For it is notoriously difficult to judge whether a tumor mass seen protruding into the mouth of a bronchoscopic tube actually represents the whole tumor or merely the top of a submerged mass, of which, like a floating iceberg, but a small portion is visible while the great bulk lies submerged.

* Presented by title before the American Surgical Association, St. Louis, Mo., May 1, 2, 3, 1940.

Bronchotomy *via* a thoracotomy opening allows accurate inspection of a growth, of its base and its extension; if palpation of the affected lobe discloses a large induration, of which it may be assumed that but a small portion has protruded into the bronchial lumen, while the main tumor lies or has extended extrabronchially, lobectomy or pneumonectomy may be undertaken at once. Otherwise the bronchus may be opened between stay sutures, the growth may be removed, its base cauterized and a portion of the bronchial wall removed with it, if necessary. The incision into the bronchus may then be repaired by suture and the chest closed, with or without drainage as seems most expedient. A long posterior thoracotomy incision with resection of the fifth rib, as described by Crafoord[2] for pneumonectomy, gives good access. The lung is retracted forward. The hilum is injected subpleurally with 15–20 cc. of ½ per cent procaine, to which epinephrine (two drops to 30 cc.) has been added. The procaine injection stops the objectionable cough reflex that follows handling of the hilar structures, and the edema resulting from the injection makes their dissection peculiarly easy. The hilar pleura is incised; the bronchial wall is steadied by two fine silk stay sutures passed through its soft posterior membranous portion and incised at a site calculated by bronchoscopic and roentgenographic observation. The lumen is inspected, the incision prolonged if necessary and the tumor removed. The incision is repaired with a single layer of fine catgut or silk sutures, including the whole thickness of the bronchial wall, care being taken to narrow the bronchial lumen as little as possible. More than one layer would be likely to lead to a stenosis. Repair of the intrapulmonary portion of the bronchus, where lung may be used to cover the suture line, is easier than that of the hilar portion. The suture need not be hermetically accurate; in the case reported it was far from so, yet the incision closed without sequela.

It would seem best in patients who cough not to attempt to cover the bronchial sutures by reuniting the incision into the hilar pleura. If the bronchus does leak air it is better that air escape into the pleura than into the mediastinum, mediastinal emphysema being a complication more difficult to handle than a pneumothorax, which is easily taken care of by a drainage tube.

The thoracotomy incision is closed; if the bronchial suture seems tight, drainage may be dispensed with, although the patient should be carefully watched for the first few days after operation and a pressure pneumothorax promptly dealt with. If there is doubt of an air leak, a catheter is introduced into the chest through a separate intercostal stab and led out under water.

Through the kindness of Dr. Cabot Brown, I was afforded the opportunity of carrying out a bronchotomy for what was thought, preoperatively, to be a benign tumor.

Case Report.—Mrs. Elise Y., age 33, was referred by Doctor Brown to the Stanford Surgical Service at the San Francisco Hospital, June 19, 1939. She had suffered for five years from chronic, intermittent obstruction of the left upper lobe, with febrile interludes, abscess formation, much cough and episodes of bleeding. A series of roentgenograms, dating from 1934 to 1937, showed intermittent obstruction of the left upper lobe. Lipiodol

injection by Doctor Brown, in April, 1939, demonstrated a round defect projecting into the bronchial lumen; at this site an obstruction was encountered bronchoscopically (Fig. 1). An abscess was drained through an interior incision in April, 1939. Bronchoscopy, four times repeated, failed to reveal a tumor and biopsies revealed nothing but shreds of inflamed bronchial mucosa. A ureteral catheter, introduced into the draining sinus of the previous thoracotomy, passed into the lower lobe bronchus beyond the site of obstruction, and a second catheter, introduced through the bronchoscope, traversed the stricture and also passed into the lower bronchus, but no ulcerative lesion, and no tumor mass, from which a biopsy could be taken, were seen. However, suspicion of a growth could not be allayed and exploratory bronchotomy was decided upon.

FIG. 1.—Bronchogram with lipiodol, April 26, 1939. Filling defect shown just above the bifurcation of the left stem bronchus.

Operation.—October 2, 1939: Under completely satisfactory anesthesia with avertin and gas, administered by Doctor Neff through an intratracheal tube, the chest was opened by Crafoord's incision; 22 cm. of the fifth rib was resected. Separation of dense adhesions offered considerable difficulty; those over the upper lobe were allowed to remain. The left lower bronchus was identified and opened between two stay sutures by a transverse incision into its membranous posterior portion; a catheter introduced into it and passed upwards met with no resistance. Upon close inspection one saw that the bronchus had been opened exactly opposite a tumor, which was attached by a pedicle to a site near the mouth of the upper lobe bronchus. As it hung down by its pedicle it occluded the upper lobe bronchus entirely and the lower lobe bronchus partially. Its anatomic situation explained its not having been visible through the bronchoscope, for coughing during the introduction of the bronchoscope had probably pushed it back into the upper lobe bronchus, where it remained hidden.

The incision was carried around at an angle so as to open the left upper bronchus; the tumor, measuring 1.5x1.4x1.2 cm., was carefully lifted up and removed by severing its pedicle with the diathermy current. The pedicle was inspected, its base cauterized again, and the incision closed with a series of fine, interrupted, chromic gut sutures

placed in one layer. The thoracotomy incision was closed, but a Pezzer catheter was placed in its posterior angle, the closure of the bronchus having seemed none too accurate.

Pathologic Diagnosis.—Dr. David Wood: Carcinoma, relatively benign.

Postoperative Course.—The catheter was submerged under water. On the second day, a small amount of subcutaneous emphysema was demonstrable over the sternal notch; a venous pressure of 21 cm. gave additional evidence of mediastinal emphysema. This, however, rapidly receded and the subsequent course was uneventful. The patient was discharged, November 2, 1939. There has been no evidence of recurrence. The left upper lobe is aerated.

FIG. 2.—Lipiodol injection 29 days after operation, October 31, 1939. Both upper and lower lobe bronchi are open. (The central density is due to previous lipiodol injections into the abscess cavity.)

Lipiodol injection, October 31, 1939, demonstrated both upper and lower left bronchi to be open (Fig. 2). Bronchoscopy several months later revealed a normal bronchial tree.

CONCLUSION

Transpleural bronchotomy is a feasible, conservative method of removing benign tumors of the bronchus, which, by reason of their anatomic situation or their doubtful extension, are not amenable to safe and certain bronchoscopic removal.

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THE REPAIR OF INGUINAL HERNIA WITH TRANSPLANTATION OF THE CORD TO THE FEMORAL CANAL*

A PRELIMINARY REPORT

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ATTEMPTS to improve the results of operations for hernia have progressed in three general directions: First, the tissues available for repair have been utilized in a number of different ways; second, many kinds of suture material have been employed; and third, various dispositions of the spermatic cord have been made. The necessity of providing room for exit of the cord has always been an obstacle to satisfactory repair. Wherever it may be placed the cord interferes to some extent with closure of the hernial defect and leaves a possible pathway for recurrence.

Bassini[1] met this problem by transferring the cord to a new position, between the internal and external oblique muscles. Halsted,[2, 3] in his earlier operations, placed it exterior to the aponeurosis of the external oblique muscle. In ten of a series of herniae in children, reported in 1895, Coley[4] allowed the cord to remain in its normal location and, in 1899, Ferguson[5] advised against altering its position in the treatment of herniae in adults. In his later operations Halsted[6] also left the cord in its natural site.

In order to reduce the size of the cord Halsted[3] at one time recommended the division of part of the spermatic veins at the point of exit. This feature of the operation was later abandoned. With the same idea in mind Torek[7] separated the elements of the cord at the internal ring and brought them out at different levels in the line of repair; the size of the opening necessary for the cord was thereby reduced. In certain cases Quain,[8] Skillern[9] and Erdman[10] have excised or divided the cremaster. Burdick[11] and his associates, in selected types of hernia, have completely divided the cord and so eliminated it as an obstacle to repair. Castration has sometimes been resorted to in older men but this procedure is not usually accepted with enthusiasm.

Cheever[12] conceived the idea of transplanting the cord to the femoral canal and, in 1923, during a discussion of certain papers[13, 14, 15] on hernia which had been presented before the American Surgical Association he called attention to the operation as follows:

"Dr. Seelig's beautiful demonstration of the futility of suturing the muscle fibers to Poupart's ligament, and Dr. Gallie's very convincing demonstration of one way to avoid it, make it reasonable, perhaps, to propose a somewhat novel method of curing inguinal hernia. Underlying all these new procedures is the widespread recognition that old methods are by no means always suc-

* Read before the American Surgical Association, St. Louis, Mo., May 3, 1940.

cessful. This new method consists in withdrawing the testicle from the scrotum, incising the transversalis fascia forming the floor of the inguinal canal and slipping the testicle down through the femoral canal beneath the ligament and between the vein and Gimbernat's ligament out through the saphenous opening and back into the scrotum. This will sound fanciful to you, but it is apparently perfectly practicable, and I have carried it out in five cases with apparent success." So far as I have been able to determine, Cheever is the first to have conceived and carried out this plan of disposition of the cord.

The possibility of utilizing the femoral canal as path of exit for the cord first suggested itself to me through the reading of an article by Fauntleroy[16] in which he described a patient whose spermatic cord was found as a congenital anomaly in the femoral canal. Apparently, the testis had followed the femoral route in its descent to the scrotum. The practicability of transferring the cord to the femoral canal was satisfactorily demonstrated on the cadaver, and I planned to try it in a suitable clinical case. Upon asking the late Dr. F. S. Mathews what he thought of such an operation I learned for the first time of Doctor Cheever's work. Encouraged by Doctor Cheever's experience with the operation, I performed, between 1929 and 1933, six operations for recurrent or large primary herniae in elderly patients, completely freeing the testicle from its scrotal attachments in each instance and then reinserting it through the femoral canal into the scrotum. The operation appeared to offer promise, but its performance presented certain technical difficulties: In freeing the testicle from the scrotum numerous small blood vessels are encountered. A second hindrance is the disproportion between the size of the testicle and the femoral canal through which it must pass; the canal in the male is usually small.

It was obvious that these difficulties could be overcome by opening the femoral canal; it would then be possible to transfer the cord without disturbing the testicle, and repair of the inguinal ligament did not appear to offer any great difficulties. With these considerations in mind the following plan of procedure was adopted:

Operative Technic.—The hernial sac is exposed through the usual incision, removed in the usual manner, and the defect in the transversalis muscle is closed (Fig. 1). The inferior as well as the superior surfaces of the inguinal (Poupart's) and lacunar (Gimbernat's) ligaments are dissected free of fat and fascia, exposing the inferior outlet of the femoral canal and the fascial sheath of the pectineus muscle near its origin (Fig. 2). The inguinal ligament is then detached by making an oblique incision along the sulcus which is formed by the inguinal aponeurotic falx (conjoined tendon) and the inguinal ligament where they are jointly attached to the pubic bone. The detachment is completed by freeing the lacunar (Gimbernat's) ligament along the line of its pubic insertion and the cord is placed in the femoral canal (Figs. 1 and 3).

The ligamentous structures are then brought over the cord and restored

to their normal relationships by means of a series of silk sutures (Figs. 4 and 5). The sutures uniting the inguinal ligament to the pubic tubercle are preferably of the mattress type. Those employed to restore the attachment to the superior pubic ramus may be simple interrupted sutures. These are passed through the ligament of the pubes (Cooper's ligament) and tied, the ends being left long (Fig. 5). The ligament which bears Cooper's[17] name was described by him as a remarkably strong ligamentous expansion extending from the tuberosity of the pubes outwards, and projecting from the bone over the iliopectineal line. The closure about the cord as it lies in the femoral canal is made snugly, and the technic is similar to the repair of a femoral hernia through the inguinal approach.

The next step in the operation is the approximation of the internal oblique muscle to the pubic (Cooper's) ligament instead of Poupart's. Goinard[18] has adopted this plan in inguinal hernioplasty because he considers Cooper's ligament the stronger of the two. The approximation is accomplished by using the long ends of the same sutures that were employed to reattach the inguinolacunar ligament to the pubic bone Fig. 6). Additional sutures are placed anterior and lateral to the femoral canal to approximate the internal oblique muscle to the inguinal ligament. We thus have the conjoined tendon and the medial portion of the internal oblique anchored to Cooper's ligament and the lateral portion of the internal oblique anchored to Poupart's. The sutures are tied and obliteration of the inguinal defect is complete (Fig. 7). The segment of cord lying between the internal inguinal ring and the femoral ring is buried and disappears from view.

The opening in the aponeurosis of the external oblique muscle is closed by imbrication, the upper leaf being brought down over the lower (Figs. 7 and 8). The sutures near the pubic tubercle may be made to include the cut end of the inguinal ligament and the integument of the bone in order to further reinforce the attachment of the ligament. Medial to the transplanted cord, the margin of the upper leaf is brought down and sutured to the pectineal fascia, and lateral to the cord it is sutured to the fascia lata (Fig. 8). The wound is then closed in the usual manner. Care should be taken to see that the testis is well down in the scrotum before the patient leaves the operating room.

The operation just described appears to be very similar to the procedure employed by Lisitsyn[19] which has recently come to my attention. In two cases reported in 1934, Lisitsyn, a Russian surgeon, divided the inguinal ligament near the pubic bone and opened the femoral canal. The cord was then placed in the canal and the ligament rejoined by suture. The aponeurosis of the external oblique muscle with the underlying tissues was sutured to the inguinal ligament and to the periosteum of the pubic bone. He then transplanted a free piece of fascia lata over the repair for reinforcement of the suture line. Lisitsyn's first operation of this kind was performed, April 3, 1929, for a recurrent hernia, and he reported that there had been no recurrence five years after operation.

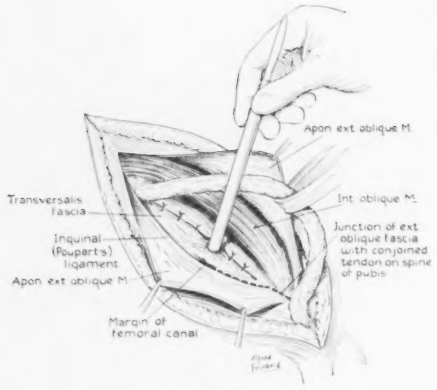
Apon ext oblique M.
Transversalis fascia
Int. oblique M.
Inguinal (Poupart's) ligament
Junction of ext. oblique fascia with conjoined tendon on spine of pubis
Apon. ext oblique M.
Margin of femoral canal

FIG. 1.

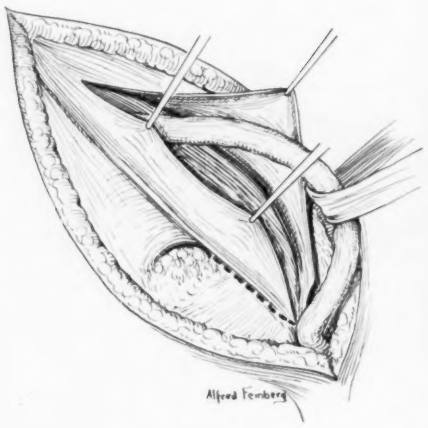

FIG. 2.

FIG. 1.—The hernial sac has been removed and the defect in the transversalis fascia sutured. The anterior margin of the femoral canal has been exposed, and the incision designed to free the inguinal (Poupart's) ligament and open the femoral canal is indicated by the dotted line. The incision is started along the junction of the aponeurotic falx (conjoined tendon) and inguinal ligament on the pubic tubercle and carried laterally, separating the ligament from its attachment to the superior pubic ramus, until the femoral canal is entered.

FIG. 2.—The inferior surface of the inguinal ligament has been cleared of fat, and the fascial sheath of the pectineus muscle and the inferior aspect of the femoral canal are exposed. The dotted line shows the course of the incision which is to free the inguinal ligament, as seen from below.

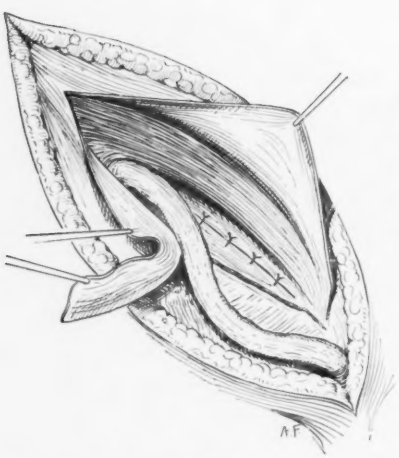

FIG. 3.

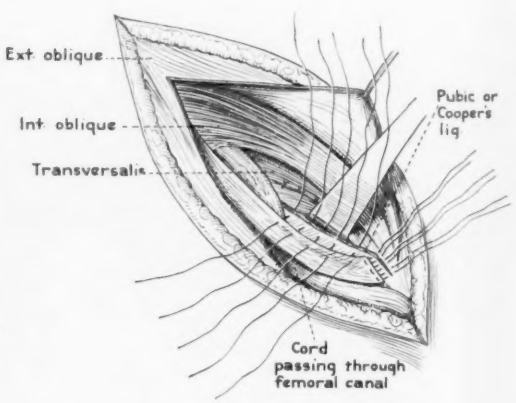

FIG. 4.

FIG. 3.—The inguinal ligament has been detached and the cord placed in the femoral canal.

FIG. 4.—Sutures have been placed to restore the ligament to its normal relationships. The anterior, or medial three sutures are of the mattress type and rejoin the ligament to the pubic tubercle. The lateral sutures are of the simple interrupted type and are designed to approximate the shelving border of the inguinal ligament to the pubic (Cooper's) ligament.

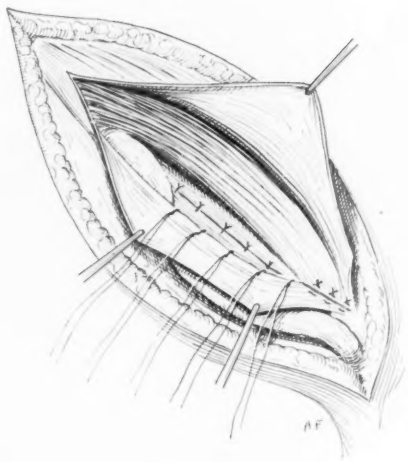

FIG. 5.

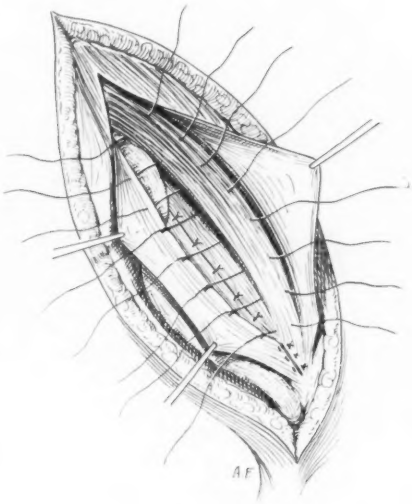

FIG. 6.

FIG. 5.—The sutures shown in Figure 4 have been tied, restoring the inguinal ligament and closing the femoral ring snugly about the cord. The ends of the lateral sutures have been left long so that they may be used to approximate the conjoined tendon and the internal oblique muscle to the pubic (Cooper's) ligament.

FIG. 6.—The long ends of the sutures shown in Figure 5 have been passed through the lower margin of the conjoined tendon and the internal oblique muscle. Additional sutures have been placed farther laterally to bring the internal oblique to the inguinal ligament.

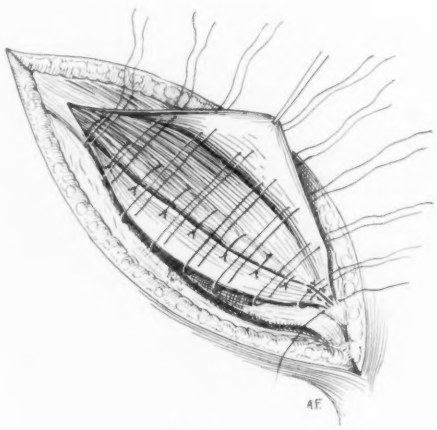

FIG. 7.

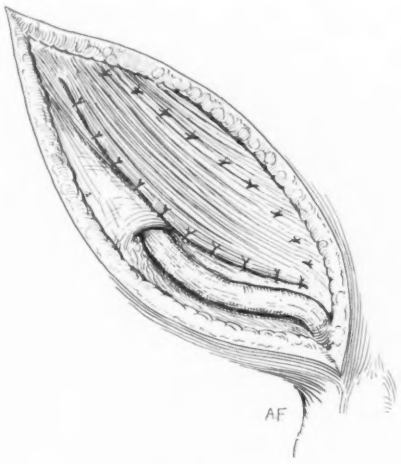

FIG. 8.

FIG. 7.—The conjoined tendon and the internal oblique muscle have been approximated to the pubic ligament medially, and to the inguinal ligament laterally. The hernial defect is completely closed. Imbricating sutures have been placed in the aponeurosis of the external oblique.

FIG. 8.—The imbricating sutures have been tied and the margin of the upper leaf has been sutured medially to the fascial sheath of the pectineus muscle and laterally to the fascia lata of the thigh.

TABLE I

REPAIR OF PRIMARY AND RECURRENT INGUINAL HERNIAE WITH TRANSPLANTATION OF CORD TO THE FEMORAL CANAL, 33 CASES

History No.	Age	Type of Hernia	Previous Repairs	Concurrent Diseases	Date of Operation	Operative Accidents	Postoperative Complications	Later Complications	Result
122–742	39	Recurrent lt. indirect, sliding—entire sigmoid	Two	None	6/24/37	Division of spermatic artery	None	Atrophy of testicle	4/10/40—well
123–653	67	Recurrent lt. indirect—incarcerated omentum	One	Chronic bronchitis	8/31/37	None	Exacerbation of bronchitis-cough	None	4/6/40—well
124–073	63	Primary rt. indirect, scrotal		Diabetes. Arteriosclerosis. Chronic myocarditis	9/29/37	None	None	None	10/25/38—well 11/29/39—Died suddenly No recurrence of hernia
148638	61	Primary rt. direct		Obesity. Arteriosclerosis. Urinary incontinence	10/5/37	None	None	None	4/7/40—well
156798	51	Primary rt. direct		None	10/14/37	None	None	None	4/7/40—well
209321	50	Recurrent lt. indirect Primary lt. femoral	One	Chronic bronchitis	7/23/38	None	Cough	None	4/7/40—femoral recurrence
209321	50	Recurrent rt. indirect	One	Chronic bronchitis	8/4/38	None	Cough	None	4/7/40—well
210770	63	Primary rt. direct		Prostatic hypertrophy	8/13/38	None	None	None	4/21/40—well
129–530	51	Primary rt. direct		None	8/17/38	None	None	None	4/24/40—well
129–680	49	Recurrent rt. direct	One	None	8/23/38	None	None	None	4/12/40—well
210770	63	Primary lt. direct		Prostatic hypertrophy	8/30/38	None	None	None	4/21/40—well

81047	48	Recurrent lt. direct	Four	Syphilis	10/18/38	Division of spermatic artery	Edema of testicle	Atrophy of testicle	4/7/40—well
218169	56	Primary rt. direct		Obesity	11/5/38	None	None	None	4/14/40—well
218977	51	Primary rt. direct		Chronic bronchitis	11/8/38	None	None	None	6/18/39—inguinal recurrence
218169	56	Primary lt. direct		Obesity	11/19/38	None	Wound infection—*Staph. aureus*	Delayed healing	4/14/40—inguinal recurrence
218977	51	Primary lt. direct		Chronic bronchitis	11/21/38	None	None	None	6/18/39—inguinal recurrence
A-10382	58	Primary lt. indirect, scrotal		Prostatic hypertrophy	12/15/38	None	Thrombophlebitis, rt. leg	None	4/10/40—well
A-09636	57	Primary lt. indirect		Hypertension. Chronic cardiovascular disease	1/10/39	None	Auricular fibrillation. Diffuse bronchitis	None	4/10/40—femoral recurrence
A-15821	53	Recurrent rt. direct and indirect, sliding	One	Slight pulmonary emphysema	3/17/39	None	Bronchopneumonia	None	4/10/40—well
A-6795	37	Recurrent rt. indirect	Two	None	10/20/39	None	Bronchopneumonia. Pulmonary tuberculosis(?)	None	4/10/40—well
A-25507	37	Recurrent rt. direct	One	None	11/6/39	None	None		Unable to locate patient
A-34208	72	Primary rt. indirect, scrotal; and rt. femoral		None	11/8/39	None	None	None	4/18/40—well
A-25507	37	Recurrent lt. direct	One	None	11/21/39	None	None		Unable to locate patient
A-34888	58	Primary lt. direct		None	12/21/39	None	Wound infection—*Staph. aureus*	None	4/10/40—well
A-15821	54	Primary lt. direct		Slight pulmonary emphysema	12/27/39	None	None	None	4/10/40—well

TABLE I (*Continued*)

History Number	Age	Type of Hernia	Previous Repairs	Concurrent Diseases	Date of Operation	Operative Accidents	Postoperative Complications	Later Complications	Result
A-35330	51	Recurrent rt. direct	Two	None	1/ 6/40	Division of spermatic artery	Edema of testicle	None	4/10/40—well
A-11085	66	Primary rt. direct and indirect, partly sliding		Prostatic hypertrophy, partial urinary retention	2/29/40	None	Edema of testicle	None	
A-36381	39	Recurrent lt. indirect, partly sliding	One	None	3/ 1/40	None	Bronchitis	None	
A-31388	60	Primary rt. direct and indirect		Pulmonary emphysema. Prostatic hypertrophy	3/ 2/40	None	Atelectasis, right lower lobe	None	
A-31390	45	Primary rt. direct		None	3/27/40	None	None	None	
A-14208	62	Primary rt. direct		Hypertensive cardiovascular disease	3/29/40	None	None	None	
A-32284	49	Primary rt. indirect, scrotal		Hypertensive cardiovascular disease. Pulmonary emphysema. Syphilis	4/ 2/40	None	None	None	
A-36480	45	Primary rt. indirect		Obesity	4/17/40	None	None		

On the surgical services of St. Luke's and New York Hospitals, transplantation of the cord to the femoral canal has been carried out in the repair of 33 inguinal herniae affecting 27 individuals since June 24, 1937 (Table I). Twenty-one herniae were primary and 12 were recurrent. Nineteen of the total number have been followed more than one year after operation; five have recurred, an incidence of approximately 26.3 per cent. In the group of 12 primary herniae, followed more than one year, there were four recurrences, or 33.3 per cent. One of the four recurrences was femoral and the remaining three were inguinal. Two of the inguinal recurrences were in one individual who had bilateral herniae (Table II). In the group of seven recurrent herniae, followed more than one year after operation, there was one recurrence, or approximately 14 per cent. This one recurrence was femoral in type and occurred in a patient who, at the time of operation, had a primary femoral as well as a recurrent inguinal hernia on the side of the subsequent recurrence (Table III). The remaining cases of the total series of 33 cases have been operated upon too recently to have any statistical value.

The apparent merits of the operation are:

(1) That it permits a complete closure of the inguinal defect without damage to the cord or testicle.

(2) It does not require any special incision or special materials.

(3) It can be applied to any type of inguinal hernia without impairment of the advantage gained by elimination of the cord as an obstacle to repair.

The most obvious disadvantages of the procedure are:

(1) Exposure of the pubic ligament is difficult in obese patients. Goinard[18] suggests use of the Reverdin needle for the placing of sutures in this ligament.

(2) It involves a detachment of the inguinal ligament. This ligament is ordinarily thought of as the sheet anchor in hernial repair and it is not heedlessly jeopardized. After the ligament has been resutured, however, one cannot doubt its stability.

(3) The advantage gained in being able to completely close the inguinal defect is offset to some extent by the necessity of opening the femoral ring. Presumably, this may give rise to a weakness at the femoral opening comparable to that produced by a femoral hernia.

It is a matter of general experience, however, that femoral hernia is less likely to recur than inguinal hernia. The incidence of recurrence in the adult males of the series reviewed by Coley[20] was 8.7 per cent for indirect, 16.4 per cent for the direct, and 11.9 per cent for the combined type of direct and indirect inguinal herniae; the recurrence rate for femoral hernia in the adult male was 9.1 per cent. Watson[21] states that 5 to 10 per cent of the indirect inguinal herniae recur, depending upon the age of the patient and the choice of operation, and that recurrences after operations for direct herniae are from 10 to 20 per cent in the hands of the most experienced operators; he places the rate of recurrence of femoral herniae, following the usual methods of repair, at slightly less than 5 per cent. This ratio of recurrence between in-

TABLE II

PRIMARY HERNIAE FOLLOWED MORE THAN ONE YEAR AFTER REPAIR, 12 CASES

History Number	Age	Type of Hernia	Concurrent Diseases	Date of Operation	Operative Accidents	Postoperative Complications	Later Complications	Result
124–073	63	Primary rt. indirect, scrotal	Diabetes. Arteriosclerosis. Chronic myocarditis	9/29/37	None	None	None	10/25/38—well. 11/29/39—died suddenly. No recurrence of hernia
148638	61	Primary rt. direct	Obesity. Arteriosclerosis. Urinary incontinence	10/ 5/37	None	None	None	4/7/40—well
156798	51	Primary rt. direct	None	10/14/37	None	None	None	4/7/40—well
210770	63	Primary rt. direct	Prostatic hypertrophy	8/13/38	None	None	None	4/21/40—well
129–530	51	Primary rt. direct	None	8/17/38	None	None	None	4/24/40—well
210770	63	Primary lt. direct	Prostatic hypertrophy	8/30/38	None	None	None	4/21/40—well
218169	56	Primary rt. direct	Obesity	11/ 5/38	None	None	None	4/14/40—well
218977	51	Primary rt. direct	Chronic bronchitis	11/ 8/38	None	None	None	6/18/39—inguinal recurrence
218169	56	Primary lt. direct	Obesity	11/19/38	None	Wound infection—*Staph. aureus*	Delayed healing	4/14/40—inguinal recurrence
218977	51	Primary lt. direct	Chronic bronchitis	11/21/38	None	None	None	6/18/39—inguinal recurrence
A-10382	58	Primary lt. indirect, scrotal	Prostatic hypertrophy	12/15/38	None	Thrombophlebitis, rt. leg	None	4/10/40—well
A-09636	57	Primary lt. indirect	Hypertension. Chronic cardiovascular disease	1/10/39	None	Auricular fibrillation. Diffuse bronchitis	None	4/10/40—femoral recurrence

TABLE III

RECURRENT HERNIAE FOLLOWED MORE THAN ONE YEAR AFTER REPAIR, SEVEN CASES

History Number	Age	Type of Hernia	Previous Repairs	Concurrent Diseases	Date of Operation	Operative Accidents	Postoperative Complications	Later Complications	Result
122–742	39	Recurrent lt. indirect, sliding—entire sigmoid	Two	None	6/24/37	Division of spermatic artery	None	Atrophy of testicle	4/10/40—well
123–653	67	Recurrent lt. indirect—incarcerated omentum	One	Chronic bronchitis	8/31/37	None	Exacerbation of bronchitis—cough	None	4/6/40—well
209321	50	Recurrent lt. indirect. Primary lt. femoral	One	Chronic bronchitis	7/23/38	None	Cough	None	4/7/40—femoral recurrence
209321	50	Recurrent rt. indirect	One	Chronic bronchitis	8/ 4/38	None	Cough	None	4/7/40—well
129–680	49	Recurrent rt. direct	One	None	8/23/38	None	None	None	4/12/40—well
81047	48	Recurrent lt. direct	Four	Syphilis	10/18/38	Division of spermatic artery	Edema of testicle	Atrophy of testicle	4/7/40—well
A-15821	53	Recurrent rt. direct and indirect, sliding	One	Slight pulmonary emphysema	3/17/39	None	Bronchopneumonia	None	4/10/40—well

guinal and femoral herniae is sometimes reversed. Glenn,[22] for example, in a series of cases from New York Hospital, found the incidence of recurrence higher in femoral than in inguinal herniae. In general, the advantage gained in being able to completely close an inguinal defect would appear to outweigh the disadvantage of producing a possible weakness at the femoral ring.

There is no reason to suppose, however, that transfer of the cord to the femoral canal will preclude its becoming a pathway for recurrence, and in two instances, already, a hernial sac has appeared in the femoral region lateral to the cord (Cases No. 209321 and No. A-09636). There is some clinical indication that the femoral recurrences are of the prevascular type described by Moschcowitz,[23] Cevario,[24] Keynes[25] and others.

The results of the operation, so far, do not warrant unrestrained optimism or complete condemnation. In estimating its value one must take into consideration the types of hernia for which it was employed. It was not undertaken in simple herniae in young patients because the operations in current use yield satisfactory results in cases of this kind. The group of 21 primary herniae, in which the operation was employed, consisted of 13 direct; four indirect scrotal; two simple indirect; one combined direct and indirect; and one direct, indirect and sliding combined. The ages of the primary group ranged from 45 to 72 years, the average being 57 years. In the recurrent group, 12 in number, there were five direct; four indirect, one of which was incarcerated; one indirect sliding; one indirect partly sliding; and one direct and indirect sliding hernia. The ages of the recurrent group ranged from 37 to 67 years of age, the average being approximately 46 years.

It is clear that the results of treatment in herniae of the kind described cannot be compared with studies which include a large proportion of less difficult types. The small series herein presented is perhaps most comparable with the cases reviewed by Grace and Johnson.[26] This review dealt with the results of hernioplasty in 1,032 patients, all of whom were more than 50 years of age. The incidence of recurrence in this large group was 25.8 per cent for primary, and 34 per cent for recurrent inguinal herniae.

The number of cases in which the cord has been transplanted to the femoral canal is not sufficiently large, and the period of observation is not long enough, to permit any conclusions as to the ultimate value of the procedure. The operation appears to be sound in principle. Further experience should reveal its weak points and possibly suggest means of correcting them.

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DISCUSSION.—DR. WILLIAM E. GALLIE (Toronto, Can.): I think we will all admit that the subject that Doctor MacFee has presented to us is very ingenious and very interesting from an anatomic standpoint. I must

confess that I was surprised to learn that the inguinal ligament could be detached from the pubic spine and sewn back in position with a restoration of the normal strength of the ligament. I would rather have expected that the ligament would remain relaxed and weak and in that way perhaps lessen the effectiveness of the attempt to cure a large recurring inguinal hernia. However, he assures me that this is not so and that actually the inguinal ligament does feel as strong as ever.

It is somewhat disturbing to find so many recurrences after the operation, but, of course, one who performs many hernioplasties must expect recurrences in large ones and particularly those who have had operations before. I suppose the place that this operation will occupy in our surgical technic will depend on experience with a large number of cases.

There are, of course, other ways of curing large recurring inguinal herniae, but I do not think it is the appropriate time to enter into that discussion; but there is one place, however, where I think this type of operation is eminently suitable. You will recall that some months ago Doctors Burdick and Coley published a paper in which they stated that they had failed to master the technic of using fascia. Now, of course, to get over the difficulty of not using fascia, because one could hardly expect them to use it, they suggested the removal of the testis and the spermatic cord in order to make the closure of the canal more easily completed. Well, it occurs to me that this is exactly the place where Doctor MacFee's procedure would be useful. When anybody feels the urge to remove the testis and the spermatic cord he should give some consideration to the suggestions that Doctor MacFee has made to-day.

THE PROBLEM OF PRODUCING COMPLETE AND LASTING SYMPATHETIC DENERVATION OF THE UPPER EXTREMITY BY PREGANGLIONIC SECTION*

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DURING the past five years (January 24, 1935–May 1, 1940) we have sympathectomized 151 upper extremities by preganglionic section for the relief of vascular spasm. We turned to this procedure because the results of cervicodorsal ganglionectomy, postganglionic section, had not been satisfactory.[1, 2] We felt that as the effects of preganglionic denervation of the lower extremity had been gratifying, there was reason to expect similar improvement if the upper extremity could be sympathectomized in a like manner.

Two difficulties have been encountered in dealing with the upper extremity which makes its successful denervation more of a problem than the lower: First, the question arises as to whether the upper extremity can be adequately sympathectomized by interruption of preganglionic pathways. Second, the matter of regeneration has given us more concern. The first question pertains to immediate results, the second to late results.

To obtain satisfactory immediate results, one must thoroughly interrupt the sympathetic pathways concerned. If sufficient residual innervation exists, this will be reflected in the clinical result. The sympathetic nerve supply to the upper extremity (Fig. 1) has been variously described,[3, 4] so that one must assume that preganglionic pathways may arise from the first to the tenth dorsal segments of the cord. The relative importance of each is unknown. The postganglionic pathways are more localized, and run from the middle cervical to the second dorsal ganglia, inclusive, to the brachial plexus. From these data it is apparent that all possible preganglionic pathways can be interrupted without dividing postganglionic fibers, with the exception of the outflow from the first dorsal segment. The latter can be abolished either by section of the first dorsal white ramus, without cutting the gray ramus, or by intraspinal section of the first dorsal anterior root. Neither of these procedures appears feasible.

We, therefore, elected to denervate the upper extremity (Fig. 2) by dividing the preganglionic outflow to the second and third dorsal ganglia of the sympathetic trunk, and sectioning the latter below the third ganglion.[5] The necessary exposure is obtained through a small vertical paravertebral incision, resecting the inner portion of the third rib and transverse process. This technic has been termed ramisectomy. A similar operation has been reported by Telford[6] who, however, uses the anterior approach.

If this operation is accurately performed, we have never been able to

* Read before the American Surgical Association, St. Louis, Mo., May 1, 2, 3, 1940.

demonstrate the presence of residual sympathetic nerve supply to the upper extremity of clinical significance. In other words, it seems quite definite that the outflow from the first dorsal segment is unimportant. This conclusion is supported by Simmons and Sheehan,[7, 8] who have studied many of Telford's cases after operation. It is further supported by our earlier experiences in which we found that the upper extremity could be thoroughly sympathectomized by excision of the second and third dorsal sympathetic ganglia and intervening trunk.

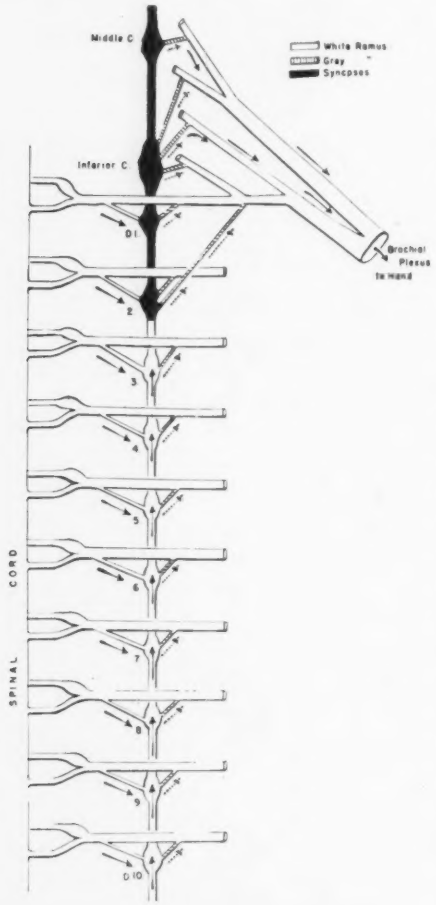

FIG. 1.—Preganglionic pathways to the arm have been described as arising from the first to the tenth dorsal segment of the cord. We have not found the outflow from D_1 to be of clinical importance. That from D_2 and D_3 is very important in some cases, and apparently of less importance in others.

If this operation is not accurately performed, incomplete sympathectomy may result. This may be due to failure to interrupt the white rami of the second or third dorsal segment or by failure to interrupt the trunk itself. We thought that by resecting the portion of the second and third intercostal nerves from which the rami arose the first possibility would be eliminated. However, in our earlier cases a number of incompletely denervated extremities resulted (Fig. 3). Subsequent study and reoperation revealed that the original operation had not been complete because of failure to interrupt the outflow from the second or third dorsal segment. The most likely explanation appeared to be that the technic did not necessarily insure division of the white rami of the two segments. We, also, soon became aware of a second difficulty because some of the extremities, which were completely denervated, began to show definite signs of regeneration, often as quickly as six months after operation.

For these reasons, the technic was changed (Fig. 4), both to insure complete denervation and to further guard against regeneration. In this modification, called extraspinal root section, the second and third intercostal nerves were resected from the lateral portion of the operative field inward, dividing the posterior and anterior roots separately at a point just proximal to the posterior root ganglion. This maneuver has been successful in pre-

venting incomplete denervation because it is impossible to fail to divide the white communicating rami when the anterior roots are always sectioned at a point proximal to their origin. It has been helpful, also, in delaying the appearance of regeneration in most instances; in preventing it in some; and in minimizing it in others. While excellent late-results have been obtained, the majority of extremities which have been denervated in this manner do show evidence of regeneration as years pass by (Fig. 5).

This is readily demonstrated by following the course of the surface temperature of a finger tip in a cool environment as time goes on, and if a fall

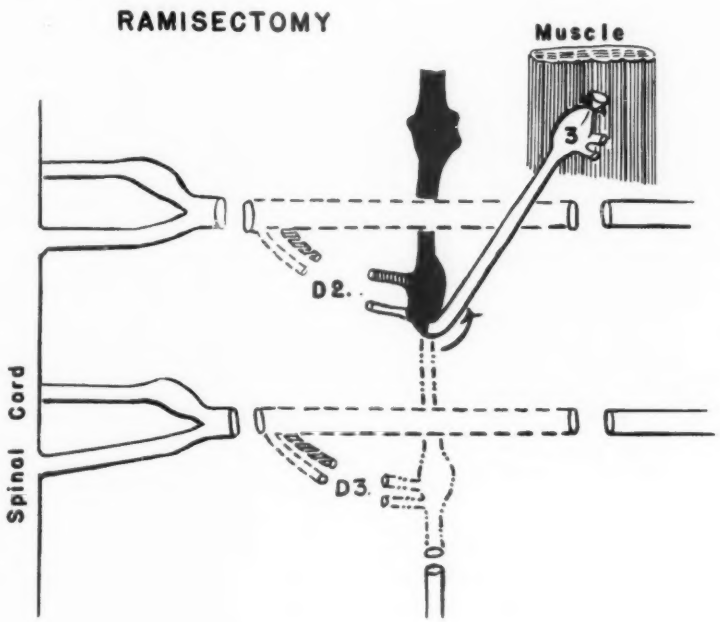

FIG. 2.—The first type of preganglionic sympathectomy was termed ramisectomy. The communicating rami of D_2 and D_3 were divided and that portion of the intercostal nerves from which they arise was resected. The sympathetic trunk was divided below D_3.

is noted, observing the subsequent rise to the previous level after regenerated pathways are temporarily interrupted again by novocain block of the appropriate peripheral nerves.

Feeling that the sectioned anterior roots of D_2 and D_3 were more likely sources of regenerating fibers than the cut end of the sympathetic trunk, the operation was further modified and termed intraspinal root section (Fig. 6). Having accidentally discovered that a large portion of the intraspinal part of the anterior root could be removed by separating the attachment of the arachnoid and then gently teasing the root out, this appeared to be a feasible routine procedure. A spinal fluid leak of no consequence results. It seemed unlikely that the proximal cut end of the roots would regenerate after the meninges

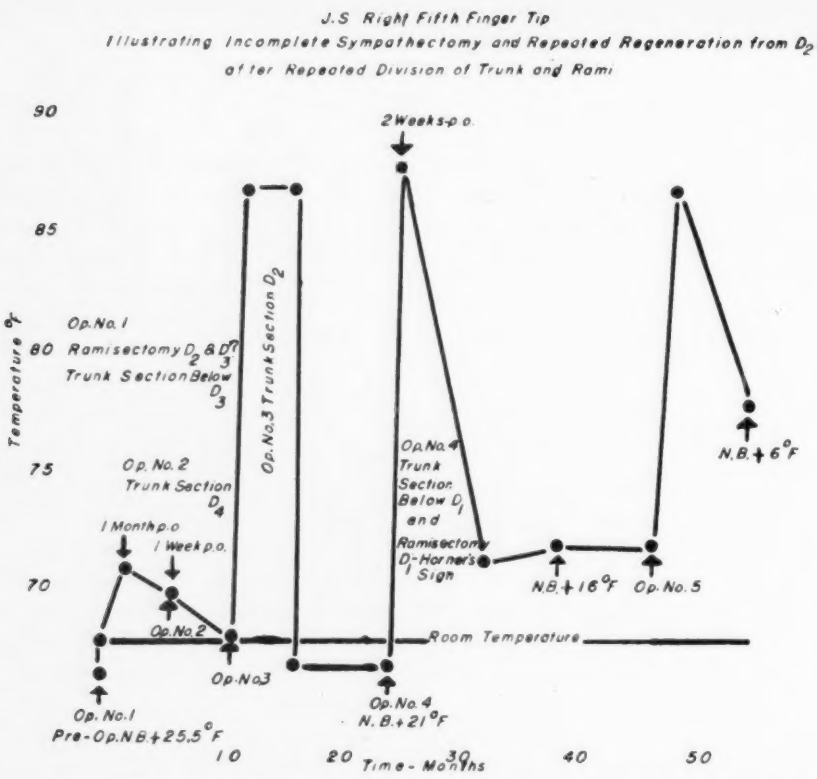

FIG. 3.—The surface temperature of a finger tip, when exposed to a cool environment, is followed over a period of five years. The first two operations were incomplete and no significant temperature rise resulted. The extremity was then sympathectomized three times by trunk section above D_2. Regeneration has taken place after each operation in six months or slightly more. The importance of the outflow from D_2 and D_3 is brought out in this case. Operation No. 5 was trunk section below C_3, by anterior approach.

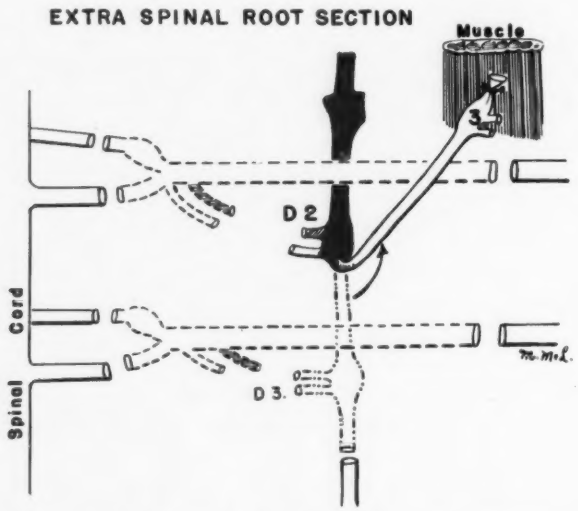

FIG. 4.—This first modification was made to insure interruption of the white rami from D_2 and D_3 by cutting the anterior roots proximal to the point of origin of the rami from the intercostal nerves. It is referred to in the text as extraspinal root section.

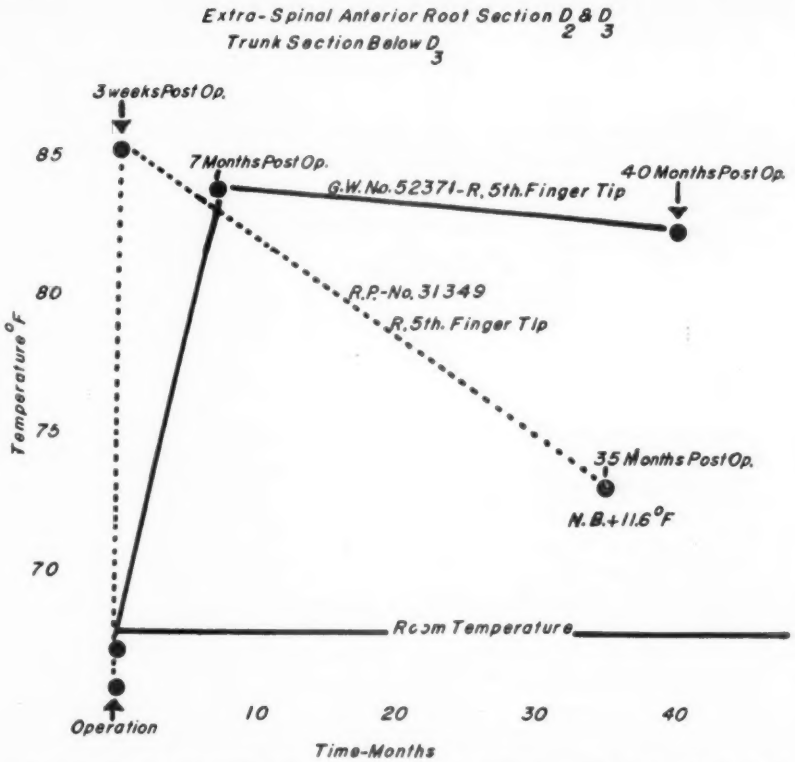

FIG. 5.—The surface temperature of a finger tip in a cool environment is followed after extraspinal root section. The same operation has been performed in each extremity (two different patients). In one instance, regeneration has taken place. In the other, there is no evidence of regeneration.

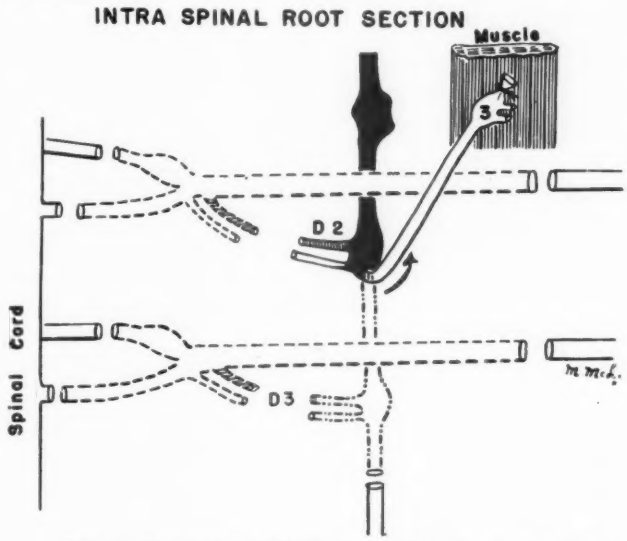

FIG. 6.—This second modification also relates to the management of the outflow from D_2 and D_3. The anterior roots are divided within the arachnoid so that the proximal cut end lies within the spinal canal rather than in the paravertebral space. It is termed intraspinal root section. It is thought to be an additional safeguard against regeneration in cases in which the outflow from D_2 and D_3 is important.

had healed (Fig. 7), because they would be contained within a water-tight compartment. The immediate effect of this operation has always been most satisfactory and complete (Fig. 8). Excellent late-results, of from two to three years' standing, also exist, but in a number of instances, moderate to marked evidence of regeneration has been detected. This, however, is usually delayed as compared with ramisectomy, and is noticed during the second year in most instances.

Some cases have had one extremity denervated by extraspinal root section and the other by intraspinal root section (Figs. 9, 10 and 11). As a rule, the results of the latter type of operation are superior, suggesting that intraspinal anterior root section is an additional safeguard against regeneration.

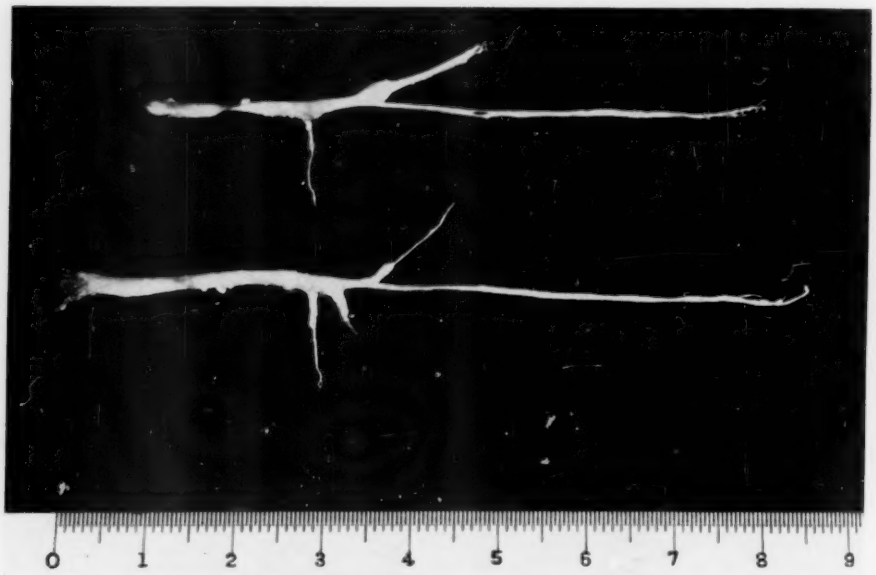

FIG. 7.—Photograph of actual specimens of the second and third intercostal nerves which have been removed, photographed beside a centimeter rule. A liberal extent of the intraspinal portion of the anterior roots is resected. The posterior root with its ganglion and the point of origin of the communicating rami from the intercostal nerves are visible.

An examination of the possible sources of regenerating fibers (Fig. 12) reveals the fact that only a few centimeters separate these from the decentralized sympathetic trunk. It seems most likely that the regenerating fibers unite with the sympathetic trunk at the second dorsal ganglion, which is not materially displaced. We have repeatedly resympathectomized regenerated extremities by sectioning the sympathetic trunk again between the first and second dorsal ganglia.

The variable results following the same operation in different patients, and different operations in the same patient, are best explained by assuming that wide variations in the origin of preganglionic pathways exist. If they come chiefly from the second and third dorsal segments, which we have proven to be the case in a number of instances, and suspect to be the case in

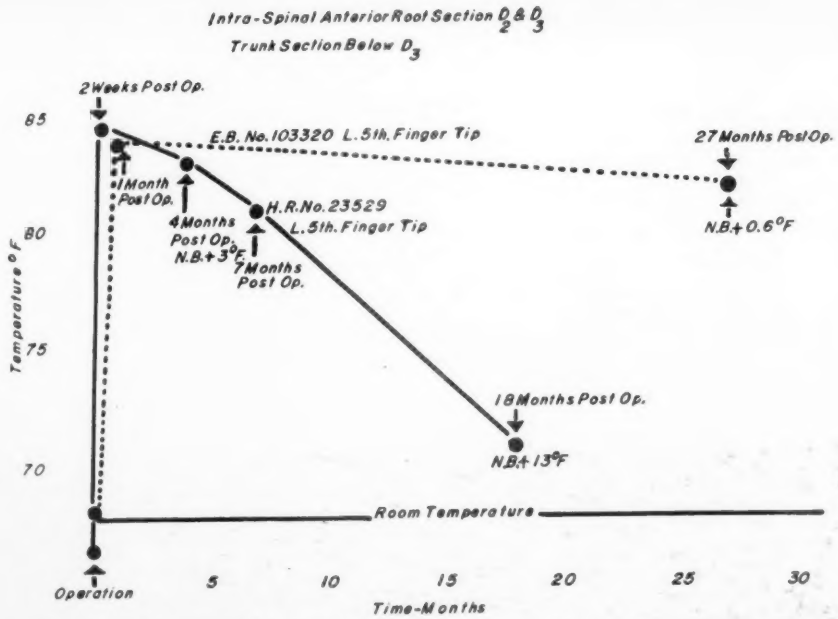

FIG. 8.—The late-result of intraspinal root section is compared in two different patients. In one instance, there is little evidence of regeneration. In the other, considerable regeneration has occurred. This probably has come largely from the sectioned end of the sympathetic trunk. It seems reasonable to believe that the outflow from D_2 and D_3 was not particularly important in the regenerated extremity.

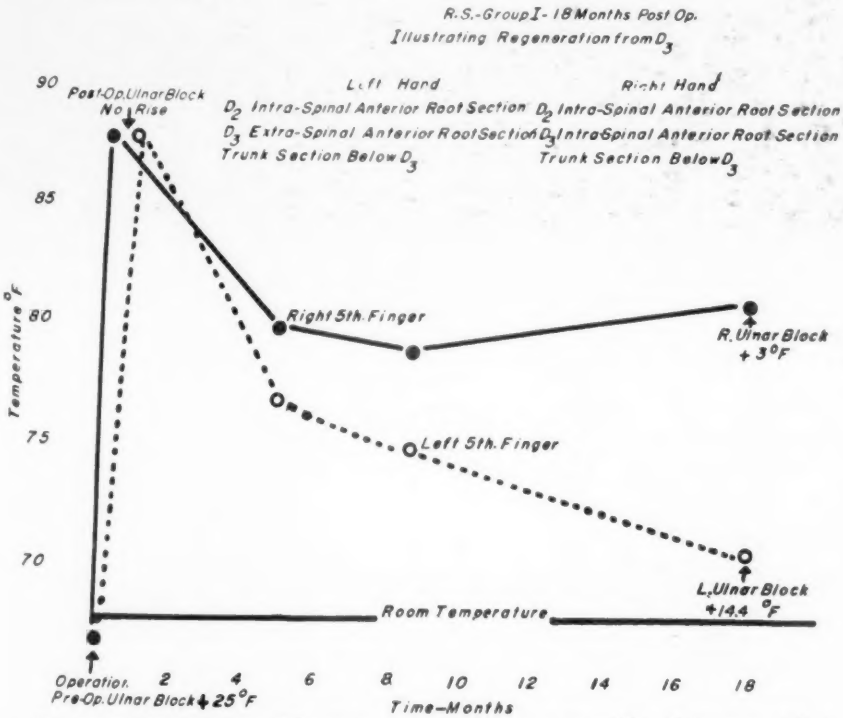

FIG. 9.—The late-results of different operations upon the two extremities of the same patient are contrasted. If it is safe to assume that the nerve supply to the arms is similar in the same case, then it is reasonable to believe that the difference in the results is due to regeneration from D_3 in this particular case. Intraspinal root section appeared to be more effective than extra-spinal root section.

the majority, great pains must be taken with the management of these two segments. One may suspect, at operation, that this is the case if the sympathetic trunk is very small. If on the other hand, the motor supply arises chiefly from lower dorsal regions of the cord, it probably makes less difference how the outflow from the upper cord is handled, and more attention must be given to the lower sectioned end of the sympathetic trunk. Obviously, simple division is not sufficient, for although this point may be as far as 5 cm.

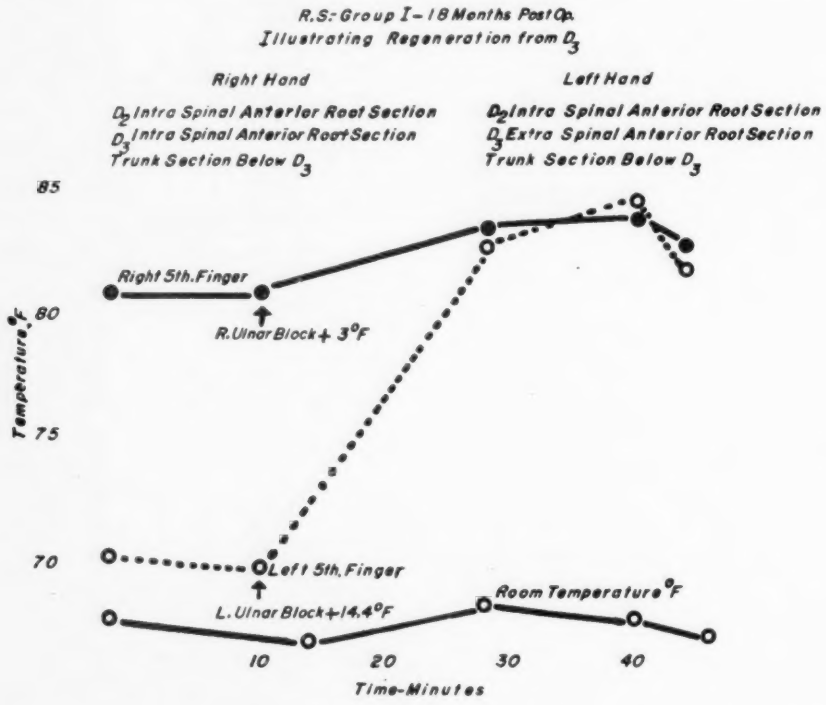

FIG. 10.—This is the same case as is illustrated in Figure 9. After novocain block of the ulnar nerves, the surface temperature of the fifth finger tips reaches the same high level, showing that any cooling which has taken place is due to nerve regeneration and not to progress of the disease. This is the usual explanation of cooling in our experience, when studying late-results.

away from the decentralized second dorsal ganglion, sympathetic fibers appear to have little difficulty in traversing this distance.

To further guard against regeneration (Fig. 13), during the past year we have carefully ligated the distal, divided end of the sympathetic trunk, a precaution which we had not formerly taken, in conjunction with the intraspinal type of anterior root section of the second and third dorsal segments. More recently, being dubious as to whether ligation of the sympathetic trunk will prove to be effective in preventing regeneration from this source, and to further guard against regeneration from D2 and D3, we have covered the decentralized second and third ganglia and intervening trunk with a fine silk cylinder. We hope that the dense scar tissue capsule, which Page[9] has found

to form in three weeks when silk is wrapped about the kidney, heart or liver, and which he believes is impervious to vessels and nerves, will form under these circumstances and prove effective in further minimizing regeneration from any of the possible sources. How successful these measures will be cannot be determined for another year or two.

Our present feeling about this problem is that the immediate and early results of preganglionic denervation of the upper extremity are uniformly satisfactory and worth while. The degree of tissue damage, or local fault, already present, is the chief limiting factor. The same is often true of the late-results, but too frequently cooling of the extremity is noted when

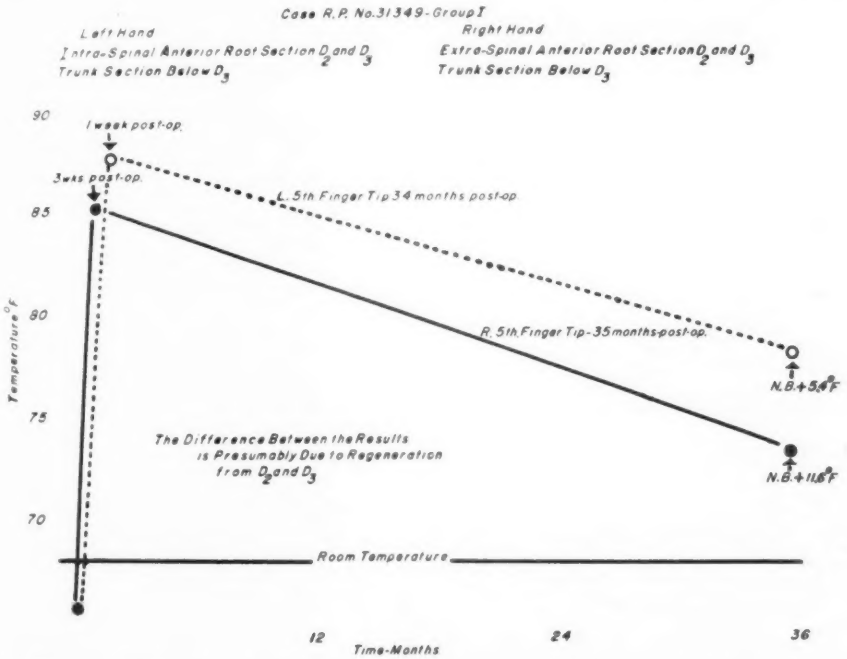

FIG. 11.—The late-result of intraspinal root section on one extremity is compared with extraspinal root section on the opposite extremity of the same patient. A minor degree of regeneration has taken place in the former, a moderate degree in the latter. Again, intraspinal root section appears to be more effective. This is usually, but not always so, suggesting that the outflow from D2 and D3 is frequently important. If, however, the outflow in a given case comes chiefly from lower dorsal levels, there would be no material difference between the two types of operation, and regeneration, if it took place, would come from the sectioned sympathetic trunk.

examined as years pass by. In the great majority of such instances this can be shown to be caused by regeneration. This may be sufficient to materially detract from the result, although one rarely finds a patient who has not benefited by operation. Even in the presence of moderate to marked regeneration (Fig. 14) patients find their symptoms milder and easier to control. A study of the circulation of such extremities, as judged by surface temperature levels in a cool environment, reveals why this is so. The regenerated extremity falls somewhere between the unoperated and the completely denervated arm. The blood flow is well sustained from the shoulder to the middorsum of the hand.

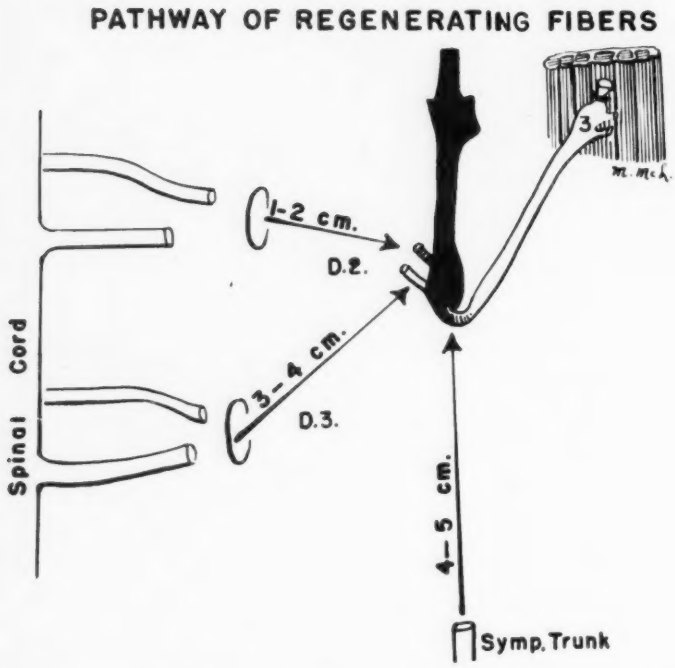

FIG. 12.—Only a few centimeters separate the three areas from which regenerating fibers may come and the decentralized, but undisplaced, second dorsal ganglion, the point where anastomosis presumably takes place. Sympathetic fibers apparently have no difficulty in covering these short distances.

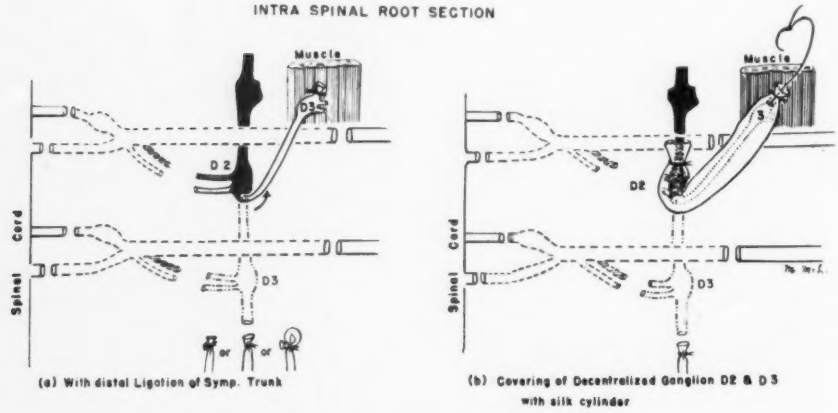

FIG. 13.—Our present technic combines intraspinal anterior root section with ligation of the distal end of the divided sympathetic trunk. More recently, the decentralized second and third ganglia and intervening trunk have been covered with a fine silk cylinder to further guard against regeneration.

Even in the presence of marked regeneration the base and midfinger temperature levels are quite high. The most marked change is in the finger tip. Regeneration is practically never complete, except in some of the earlier cases denervated by ramisectomy and trunk section.

Because of the uniformly gratifying immediate and early results,[10] and because equally satisfactory late-results have been obtained, it seems desirable to persist in the attempt to prevent and further minimize regeneration which is the principal cause of inferior late-results. It is perhaps not too much to

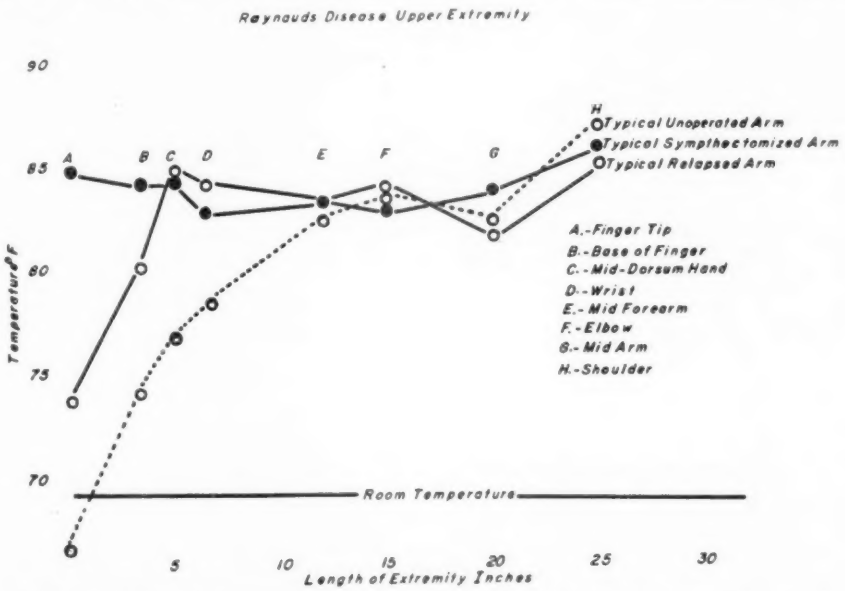

FIG. 14.—When the vasospastic upper extremity is exposed to a cool environment, and surface temperatures are recorded at frequent intervals from the finger tip to the shoulder, a characteristic curve results. The temperature is well sustained from the shoulder to the upper third of the forearm. It then falls abruptly, so that the finger tip is generally below the room temperature. When sympathectomy is complete, a high surface temperature is found. Almost the same level is maintained from finger tip to shoulder, except when marked organic disease exists before operation. When regeneration of moderate to marked degree is found, the surface temperatures are sustained from shoulder to midhand. From there, distally, cooling is noted to be most marked at the finger tip. This usually, however, still remains above room temperature, and the relapsed extremity resembles a normal extremity examined under the same circumstances. These findings are in accord with the late clinical results, which are beneficial to the patient even if definite evidence of regeneration can be demonstrated. The latter is rarely complete.

expect that this difficulty either may have been or can be solved without increasing the magnitude or risk of the operation.

CONCLUSIONS

(1) The upper extremity can be thoroughly sympathectomized by interrupting the outflow from the second and third dorsal segments and dividing the sympathetic trunk below its third ganglion. The outflow from D1 is not important in man.

(2) The immediate results are uniformly satisfactory. The late-results are variable. This is due to cooling of the extremity, which in most instances is caused by regeneration of sympathetic motor nerves.

(3) A number of variations in surgical technic are discussed. These changes have been made primarily to guard against regeneration.

(4) Even in the presence of a considerable degree of regeneration, the blood flow to the extremity is improved, and the result worth while from the patient's point of view. Regeneration is rarely complete.

(5) It seems reasonable to expect that further precautions which have or can be taken against regeneration will make the late-results even more satisfactory.

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DISCUSSION.—DR. PETER HEINBECKER (St. Louis, Mo.): We envy the richness of Doctor Smithwick's experience. Mere volume of work, in itself, would not be significant in this field. His contributions to the body of knowledge governing the treatment of spastic vascular disease have contained many significant physiologic observations. We hope that he will not take amiss the temerity which leads us to differ with certain of his concepts. Concepts determine the course of modifications in treatment.

Spastic vascular disease is regarded by Lewis and coworkers as a primary disease of the blood vessel musculature. In this we concur, and we believe that evidence has been furnished by us to show that the blood vessels of individuals so afflicted respond hyperdynamically to nervous and to humoral influences. The disease may, in itself, be progressive but, ordinarily, its progress is modified by such influences. It is not believed that the disease is due to a primary hyperfunction of vasomotor nerve centers. It is easily understood, then, that we are loath to interpret progression of the disease, after a proper sympathectomy, as due to regeneration of autonomic nerve fibers. The criterion for such regeneration is often the supposed return of varying degrees of sweat gland function. Is it certain that the tests employed do not yield a positive result from the secretion of sebaceous glands and from the loss of insensible perspiration? Doctor Smithwick has secured evidence of a

rise in temperature of the fifth finger, after appropriate nerve blocking. This could be interpreted as the result of an incomplete denervation (D1 interruption omitted), which makes itself manifest after sensitization from partial denervation has had time to develop instead of considering it an expression of sympathetic nerve fiber regeneration.

Sympathetic nerve fiber regeneration following postganglionic denervation (removal of ganglia) could at its maximum be trifling. The ratio of pre- to postganglionic fibers in regions where it has been investigated has been found to be about 1 to 30. If, then, all preganglionic fibers could be supposed to find their way to an end-organ, the effect could not be more than one-thirtieth of the normal. Direct action of regenerated preganglionic neurons on effector organs has never been demonstrated. In the preganglionic type of denervation some of the fibers, possibly, could connect again with postganglionic neurons and in this way exert a greater influence. All our clinical reports indicate that preganglionic denervation results in fewer signs of regeneration than does postganglionic denervation. There is no *a priori* reason why regeneration should not occur, also, following lower extremity ganglionectomy with equal facility as in upper extremity operations. No one will deny that the end-results of lower extremity operations are very much better than those following upper extremity operations. The explanation, therefore, probably does not reside in the regeneration factor at all. To add further difficulty to the theory of regeneration when needed to explain a return of sweating, it might be stated that the investigation of André Thomas led him to the conclusion that the arm and upper chest segments derived their nerve supply for sweat glands from D5 to D7. In most operations now performed, the sympathetic trunk is cut below D3 and elevated several inches in the wound. This would certainly make regeneration from levels D5 to D7 a hazardous adventure.

It is the belief in our clinic that the upper extremity is not denervated completely unless the sympathetic fibers from D1 are eliminated. Man's organization is a modified metameric one. It seems likely, then, that sympathetic fibers from a particular root level would at least supply that level no matter what other levels it might supply. Our belief is based also on the excellent anatomic studies by Albert Kountz in the dog and in the cat, in which he has shown that as much as 50 per cent of the sympathetic outflow to the arm may come from D1. The burden of proof would appear to rest on anyone accepting the idea that man differs materially from these animals in his nerve fiber distribution.

It is granted that preganglionic denervation is preferable to postganglionic denervation because the sensitization to epinephrine of the blood vessels, denervated preganglionically, is less.

It has been shown, recently, by Homer Smith, that in the prone position the circulation of the kidney functionally denervated by spinal anesthesia is not increased over the normal. As soon as the upright position is assumed, vasoconstrictor influences become effective in cutting down the renal blood flow. This indicates that in the upright position vasoconstrictor influences exerted on the blood vessels of the lower extremity are most active. It seems reasonable to assume that such vasoconstrictor influences, whose measure is dependent upon posture, would be much greater in the lower than in the upper extremities. Hertzmann, of St. Louis, has found that, in the semireclining position, the blood flow through the toes is always less than in the fingers. To the extent that this is due to nervous influences, denervation of the lower extremities would then eliminate vasoconstrictor influences of greater magnitude than in the upper extremity. In this resides, in our opinion, the main

reason for the better clinical results of operations on the lower extremity than on the upper in cases of spastic vascular disease.

Dr. James C. White (Boston, Mass.): I think that this work depends so much on underlying animal physiology that it should be worth while to spend just a moment to review the experiments upon which it was based. We know the modern physiologic concept that nerve impulses are conducted electrically over the nerve, but that a chemical substance propagates the discharge from the nerve ending to the muscle fibers. Furthermore, when the nerve fiber degenerates, the action of the chemical substance on the denervated neuro-effector mechanism becomes greatly intensified. This principle of sensitization applies not only to the sympathetic system, where adrenalin and sympathin are the chemical factors, but also to the parasympathetic, where acetylcholine is the chemical mediator.

The best way to show how important this is is to take a monkey and denervate his arm by cutting all the anterior thoracic nerve roots from the second down to about the tenth. Those are the ones that give off the vasoconstrictor impulses. You do not have to cut the first. Having done that, follow the skin temperature of the fingers as the monkey becomes excited or as he reacts to a small dose of adrenalin. His hands cool off very little. Then take that monkey and resect the inferior cervical and first and second thoracic ganglia on the same side. His hand will then cool markedly as soon as he gets excited or is injected with adrenalin. Peter Ashcroft, working in Doctor Fulton's laboratory in New Haven, has shown the same phenomenon in the lower extremity.

Now, in the second place, about the tendency of these structures to regenerate: Here again, animal work has a great deal to show. Dr. Ferdinand Lee, at Johns Hopkins, pointed out that when the cervical sympathetic chain is cut and the two ends placed on opposite sides of the sternomastoid, the pupillary reactions return within a period of four weeks, and in serial sections through the muscle, regenerating axones can be followed across the gap.

An effective sympathectomy, in addition to eliminating the possibility of regeneration, must cut all the nerve fibers to a given area. Recent work, in Doctor Cannon's laboratory by Doctor Simeone, has shown that even if you destroy 90 per cent of the innervation of the smooth muscle, the remaining 10 per cent of the fibers, by secreting sympathin at their endings, can fire off the paralyzed portion of the muscle. So your operation must not only prevent regeneration but it must be a complete sympathectomy in addition.

In the third place, it does not seem fair to apply finer physiologic points from animals to man. That is particularly true in neurology, and just because you can show vasoconstrictor fibers to the arm in the first thoracic nerve of the cat or dog, does not necessarily prove their presence in human beings. So far as I know Doctor Heinbecker and Doctor Kuntz have no evidence to show that the first thoracic nerve carries important vasoconstrictor or sudomotor fibers to the arm in man.

There are a great many new tests which have been put into general use for testing regeneration—determination of electrical skin resistance in ohms, measurements of the minute vasoconstriction that can be observed with the finger plethysmograph. When postoperative patients are followed in this way, one can really determine when regeneration has taker place, but, so far, these tests have not been in general use in other clinics.

Because of the extraordinary tendency of the preganglionic fibers to regenerate this new operation for Raynaud's disease has been fraught with great difficulty. I think Doctor Smithwick deserves extraordinary credit for over-

coming these difficulties, and it is really fair to say that at the end of a year, or even two years, after preganglionic denervation of the upper, as well as the lower extremities, many of the hands of his patients are just as warm as the feet.

DR. MAX M. PEET (Ann Arbor, Mich.): I feel that those of us who are performing neurosurgery owe a big debt of gratitude to Doctor Smithwick and Doctor White for the work that they have been doing, particularly to point out the difference in the final action between pre- and postganglionic sympathectomy. At our various neurologic surgical meetings we frequently argued as to why we obtained such good results in the lower extremities by lumbar sympathectomy and almost uniformly got poorer results in the upper. The latter patient is improved, but on exposure to cold and particularly under excitement or mental stress, there develops a certain amount of vasoconstriction. I think it rarely tended to the point of gangrene in the finger tips, but it was rather common that vascular constriction would be sufficient to cause blanching of the fingers and many times pain.

So, when Smithwick first brought out this idea, really originating, of course, in Cannon's laboratory, that the preganglionic section did not make those blood vessels particularly sensitive to circulating adrenalin and sympathin, we immediately took up that approach ourselves. I visited Doctor Smithwick, watched him operate, and talked it over in detail. We have been following his technic since. I realize that there is probably no part of the nervous system that regenerates as readily as does the sympathetic. The fifth nerve, peripheral to the gasserian ganglion, is possibly an exception, but we have overcome this difficulty by section of the nerve central to its ganglion.

As to how we are going to overcome these regeneration tendencies of the sympathetic nerves I am not certain, but they do not always regenerate, and we have had some cases that have apparently remained permanently cured. There is no question, in my mind, that the first thoracic nerve does not supply sympathetic fibers to the arm. We have tested many of these patients by the sweating test, and there has been no evidence whatever that sympathetic fibers to the arm come off with the first thoracic. There is much evidence that the fibers do come off the second, third, and even down as low as the twelfth thoracic.

We have had patients who developed Raynaud's disease from a proven lesion in the brain. This I think proves, quite conclusively, that this may be a disease of central origin and not a local disease of the blood vessel. True, after Raynaud's disease has advanced sufficiently you do get local disease in the peripheral vessels, but as a primary disease I think it is one of the central nervous system. The object of the whole operation is to break the connection between the central nervous system, or at least the spinal cord, and the peripheral vessels. Doctor Smithwick's procedure has been very efficient except for the tendency to regeneration. I think perhaps he has overcome that.

DR. REGINALD H. SMITHWICK (Boston, Mass.): I dislike to bring up, at this time, the question of the etiology of this disease because ever since Raynaud described it in 1860, it has been a very fruitful subject for argument and, apparently, still is, and perhaps in our present state of ignorance it is less important to know the etiology of the disease than to be able to select cases in which you can prove beforehand that something really worth while can be accomplished for the patient. Of course, time did not permit me to speak of the type of cases in which this operation was performed, but over two-thirds of them had considerable evidence of local fault as described by Sir Thomas

Lewis, either as the result of long-standing vascular spasm, or because the vascular spasm was known to be secondary to some organic disease of the vessel, such as sudden occlusion of major arteries, thrombo-angiitis obliterans, arteriosclerosis, and various other lesions. I can say that, providing regeneration is prevented, these patients with definite organic changes have obtained some of the best results in the series, and I disagree with those who would limit the field of application of such a procedure to only the very earliest cases without evidence of organic change.

Time, of course, did not permit me to summarize our evidence for the fact that D1 is not of importance in man. Doctor White and Doctor Heinbecker have pointed out that the evidence on which the supposition that D1 is of importance, comes largely from animals. While one can draw conclusions from animals to man in certain regards, it certainly is very dangerous to do so as far as anatomy is concerned. The evidence which we have on this point was presented in detail a year ago here in St. Louis and published early this year.

I regret to bring up the matter of the lower extremity because it really has not much to do with the upper extremity, as far as this discussion goes, but I can say that we have almost as many cases that have regenerated in the lower extremity as we have in the upper extremity and that regeneration there is a very important problem. Even though one can undertake a much more radical procedure from the point of view of separation of the divided ends of the trunk in the lumbar region than in the dorsal region, nevertheless, as we follow our late cases four, five, six, eight, ten years after operation and check on them very carefully, we realize that a very high percentage of them have significant evidence of regeneration.

To my mind, we have passed the point where it is a question of knowing what to do in order to denervate either the arm or the leg. We understand that well, and obtain many good, lasting, worth while results. The chief problem to-day is to prevent regeneration and, as far as I know, nobody has ever found a way to do that as yet.

A RÔLE FOR SURGEONS IN THE PROBLEM OF ESSENTIAL HYPERTENSION*

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CONFLICTING EVALUATIONS of the result of splanchnic section for essential hypertension are being made. In spite of the enthusiasm of the surgeon, the internist has not been convinced of its efficacy. The availability in this field of follow-up results of longer duration (Craig and Adson, 1939; Peet, 1939; Heinbecker, unpublished data), together with a better understanding of the pathologic physiology of hypertension, makes possible this analysis in which an attempt will be made to outline a rôle for surgeons dealing with the problem of essential hypertension in man. In a subject of such rapid development as our knowledge of the control of blood pressure, one must face the possibility of reading with a sense of embarrassment at some later date what one now writes with full confidence. The outlook for the discovery of a substance to neutralize the action of agents known to decrease the caliber of blood vessels in the state of hypertension in man is not too fanciful to be entertained.

FACTORS IN NORMAL BLOOD PRESSURE CONTROL

Blood pressure is determined by the cardiac output and the peripheral resistance of the vascular tree. The latter is dependent, primarily, upon the caliber of the terminal arterioles. These possess an inherent tone which is subject to modifications by nervous and by humoral influences.

Rôle of the Nervous System.—The nervous control of the size of blood vessels is one of the most essential regulatory systems in the body. Special moderator sense organs located in the walls of the aorta, the carotid sinuses, in the mesentery and, possibly, throughout the blood vessels of the body respond to variations in pressure within the vessels by discharging impulses whose frequency closely follows fluctuations of arterial pressure. These impulses are transmitted to the cardiovascular medullary centers, and from these centers over the sympathetic and parasympathetic nerves a stream of impulses modifies the tone and thereby the caliber of the blood vessels. They modify, also, the rate and force of the heart beat. A rise in pressure results in a decrease of the vasoconstrictor impulses, a slowing of the heart and an increase of vasodilator influences. A fall in pressure results in an increase in vasoconstrictor impulses, a decrease of vagal inhibition of the heart and a diminution of vasodilator impulses. The circulation in the normal individual is thus largely self-controlled.

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It is believed by Smith (1939) that under basal resting conditions the normal renal blood flow in man is not tonically affected by nervous influences. In the upright position reflex vasoconstrictor influences narrow the afferent arterioles of the kidney appreciably as shown by a decrease in renal plasma flow at a time when the mean arterial pressure is not decreased. There is a concomitant fall in the filtration fraction, indicating that the constriction is in the afferent rather than in the efferent arterioles.

Rôle of the Endocrines.—The degree to which the caliber of the blood vessels is normally modified by the secretions of the endocrine glands is less definitely known. Loss of the adrenal glands, especially their cortical division, is associated with generalized hypotonicity of all body musculature and with hypotension. The inference seems justified that these hormones normally aid in maintaining blood vessel tone. Pituitary hormones may also play a rôle because total hypophysectomy tends to lower blood pressure somewhat (White and Heinbecker, unpublished data). This may, however, in whole or in part, be a consequence of a diminished cardiac output because White and Heinbecker (1940) have shown that at certain periods following hypophysectomy the diodrast plasma clearance and, therefore, presumably the renal blood flow are diminished as much as 50 per cent.

Rôle of the Kidney.—The recent demonstration that the ischemic kidney releases a pressor substance (Harrison, Blalock, Mason and Williams, 1936) suggests that the normal kidney may have, within itself, the mechanism for the secretion of humoral substances which can insure the normality of its own blood flow by modifying the caliber of the blood vessels of the kidney and the body generally. The actual status of this mechanism in the control of blood pressure in the normal individual remains to be established.

BLOOD PRESSURE IN HYPERTENSION

The blood pressure changes in essential hypertension are characterized by a rise in both diastolic and systolic pressures. In order that the diagnosis be made, the diastolic pressure must be raised. There is general agreement that some measure of hypertension exists when the diastolic pressure is 100 Mm.Hg. or over. This is effected by a generalized vasoconstriction as it has been amply demonstrated that cardiac output (stroke volume x heart rate) is not modified in essential hypertension. Other factors such as blood volume and blood viscosity are also normal.

The State of the Arteries in Hypertension.—The assumption is too often made that the vascular musculature of all persons has identical physiologic properties. Evidence, much of which, it is true, cannot be easily subjected to rigid experimental tests, is, nevertheless, at hand to suggest that the responsiveness of vascular smooth musculature to nervous and humoral influences may vary quantitatively if not qualitatively in different individuals. The basis for such variations in responsiveness is regarded as genetic or constitutional and its nature is not known. This concept is supported by the evidence of a marked difference in the circulatory response of different in-

dividuals on exposure to cold (Hines and Brown, 1933) and to exogenous epinephrine (Jensen, 1930). It is also supported by the evidence that in persons exhibiting the Raynaud syndrome (Heinbecker and Bishop, 1938) the blood vessels respond hyperdynamically to nervous and to humoral influences when compared with other individuals.

On the other hand, there is evidence that environmental factors are required to bring out a constitutional predisposition to hypertension. Thus, African Negroes of similar strain to the imported North American Negroes have little or no hypertension while in America Negroes have hypertension in increasing degrees (Donison, 1929, and Allen, 1931). This can be interpreted as indicating that certain of the imported individuals were of the type possessing blood vessels with an inherent tendency to respond hyperdynamically to vasopressor influences; these individuals, when placed under environmental circumstances which increased such influences, developed hypertension. Statistics reveal that persons, one or both of whose parents had essential hypertension, have a much greater tendency to develop hypertension than do persons neither of whose parents had hypertension (Weitz, 1926). The inference must not be made that this is an instance of the inheritance of acquired characteristics, as geneticists deny the possibility. What is inherited is the degree of responsiveness of their blood vessel musculature to vasopressor influences. In the author's opinion an analysis of those environmental factors known to modify blood pressure and which the American Negro, especially the city dweller, is subjected to in greater degree than the African Negro leads to the impression that the most important ones act through the nervous system. Such nervous influences could narrow the blood vessel caliber directly, or indirectly, through humoral influences. Hypertension could presumably result if such action brought about constriction of the renal vessels.

Neurogenic Factors in Essential Hypertension.—The impression that neurogenic factors are in themselves always responsible for the generalized vasoconstriction of essential hypertension can no longer be entertained. This is evident from the failure of extensive sympathectomy in humans to lower the blood pressure at a time when generalized and renal arterial degeneration is not marked. That they may, however, play a rôle is evident from those case reports in which a definite and sustained drop in diastolic pressure has followed splanchnic section. That other factors can bring about hypertension is shown by the reports of cases in which the blood pressure has risen following a temporary lowering from splanchnic section where nerve regeneration can be excluded. Experimental evidence that hypertension of renal origin can be effected through nervous influences has been afforded by Heymans and his associates, in dogs (Grimson, Bouckaert and Heymans, 1939). These investigators produced a prolonged rise in blood pressure in animals in which sympathectomy, except for the nerves to the kidneys and adrenals, was complete and in which the moderator nerves from the carotid arteries and the aorta were removed. No hypertension developed in animals so

treated with the moderator nerves intact. The hypertension was eliminated when the nerve supply to the kidneys was removed. Their results demonstrate that the kidney can play an essential rôle in the development of hypertension and that a nervous mechanism can initiate the process in the kidney which leads to hypertension.

No cogent evidence exists to indicate that a defect in function of the moderator mechanism is the cause of hypertension in man. Gannon (1936), Pickering, Kissin and Rothschild (1936) have shown that in persons with hypertension, pressure on the carotid sinus produces as much slowing of the pulse and drop in blod pressure as in normal individuals. It is true, however, in the large majority of cases of essential hypertension that there is an absence of bradycardia during sudden rises of blood pressure. At present the mechanism for this remains unclear.

There remains the possibility that the action of the central nervous system, especially of the diencephalon, in initiating vasoconstrictor impulses is exaggerated in its response to the extrinsic and intrinsic stimuli reaching it under the conditions of man's existence in modern civilization (Raab, 1931). More evidence is desirable before the acceptance of this hypothesis.

Endocrine Factors in Hypertension.—Normally, under basal conditions the caliber of peripheral arterioles is not known to be greatly modified by the products of the endocrine glands except in the case of the adrenal cortex. The presence of an excess amount of epinephrine or of adrenal cortical hormone such as is found in the presence of tumors of these structures may result in hypertension of the essential type which is completely relieved by removal of the tumor.

Cushing's (1932) description of pituitary basophilism has pointed to a possible constrictor rôle of one of the pituitary hormones when present in an excess amount but, so far, no proof of the existence of such a hormone has been presented. It is suspected by some that the effect may be an indirect one through the adrenal cortex. It seems probable that the action of the hormones of the adrenal and of the pituitary gland in the mechanism of human hypertension is synergistic with that of a pressor substance from the kidney.

The Rôle of the Kidney in Hypertension.—From the very beginning of our attention to blood pressure, clinical studies have indicated that the kidney may play an important rôle in hypertension. There has been controversy about whether the renal pathology is primary or secondary. The recent work of Goldblatt and his associates (1934, and subsequent papers) appears to have answered this question in their demonstration that renal ischemia leads not only to hypertension but also to occlusive disease of the blood vessels of those organs of the body in which pathologic studies on human cases of essential hypertension have shown such lesions to exist. That such lesions could not be expected to be present in the kidney under Goldblatt's experimental conditions is obvious because in that organ the blood pressure is low due to the clamp placed on the renal artery. This, in itself, seems good evidence that the continued hypertension has led to the occlusive disease in the other arteries. The

mechanism of the development of hypertension by the ischemic kidney has been investigated by Goldblatt (1934, *loc. cit.*) by Page and Hilmer (1940) and others. An analysis of their results indicates that the ischemic kidney releases a pressor substance such as was designated "renin" by Tigerstedt and Bergman (1898). This leads to the production of a generalized vasoconstriction. Admittedly, there are many who do not consider it proven that in human essential hypertension this is the mechanism of the hypertension. There is no established mechanism to account for the initiation of the renal ischemia. The lack of an explanation of its origin does not invalidate the excellent physiologic evidence that such ischemia is possible. The studies of Smith (1939, *loc. cit.*) and of Findley and White (unpublished data) show that in patients with early hypertensive disease, before clinical evidence of renal damage is obvious, there is, nevertheless, a diminished renal blood flow. Smith finds that the diminution in tubular function is sometimes less than is the diminution in blood flow. This suggests that the diminution of vascular function is primary in time and that the disturbance in tubular function is the result rather than the cause of renal ischemia. The results of these workers further indicate that the immediate disturbance of function is a constriction of the efferent glomerular arteries. This is similar to the effect on the kidney vessels produced by epinephrine and by renin (Corcoran and Page, 1939).

That the Goldblatt principle plays a primary rôle in some forms of human hypertension is definitely shown by the demonstration that all signs of the disease are in some instances obliterated by removal of a single diseased kidney (Barker and Walters, 1938). A basis for an impairment of the renal blood flow exists in other forms of renal disease associated with hypertension—in inflammatory diseases of the kidney, in the vascular changes of old age, and in the obstructive lesions of the lower urinary tract where pressure changes in the kidney would be expected to be reflected on the renal blood vessels.

The demonstration that relief from renal ischemia will result in the elimination of all signs of the disease in man would incriminate the kidney as a primary factor in hypertension beyond any doubt. One way in which this might be accomplished is by renal denervation. If such a result followed, it would answer the question as to whether or not nervous influences are responsible for the initial vasoconstriction of the kidney vessels. While it is the author's opinion, based on clinical observations, that such influences will be found responsible for the initial vasoconstriction in many cases, it is felt probable that in other cases humoral influences will be found to play that rôle. The possibility also exists that hypertension follows from a disease process which is primary in blood vessels, particularly the renal blood vessels, of a type in which functional narrowing is a first manifestation, with later spontaneous progression to an occlusive stage. This seems to be the course of events in certain cases of spastic vascular disease of the extremities (Heinbecker and Bishop, 1938, *loc. cit.*). Here, nervous and humoral influences merely modify the rate of progression of the disease process which may never become of clinical significance without them. Such a disease process may be based on a constitutional tend-

ency of the blood vessels of certain individuals to respond hyperdynamically to normal nervous or humoral influences. Any excess of such influences over the normal would exaggerate the blood vessel constriction. Such functional constriction would doubtlessly involve the vasa vasorum and might, thereby, lead to degenerative changes in the intimal and subintimal layers by interference with their blood supply. Evidence in support of such a hypothesis has been furnished recently by Winternitz, Thomas and LeCompte (1938) in their discussion of the biology of arteriosclerosis.

Synergistic Action of a Renal Substance and Epinephrine.—From an analysis of our end-results of splanchnic section in humans, it was evident that symptomatic relief from headache, from a sense of cardiac oppression and from restlessness was obtained in cases in which there was no lowering of the blood pressure. Inasmuch as the operation denervates the adrenals as well as the kidneys, it was suspected that the adrenal denervation might be responsible for such relief in persons with hypertension. It was known that adrenal denervation lowers the amount of circulating epinephrine. No direct evidence of the effect of this on the properties of nerve elements in the body was available. However, a depression of nervous reactions by extensive sympathectomy in otherwise normal animals has been demonstrated by Hines and Brown (1933, *loc. cit.*). It seems reasonable to assume that this depression resulted from the adrenal denervation. A similar result should follow in man. The fact that in a high percentage of cases in persons with hypertension the reaction to cold is exaggerated, as it also is to intravenous exogenous epinephrine, led to the suspicion that in such persons the mechanism leading to hypertension might increase coincidentally the effect of epinephrine on their smooth musculature.

Experimental Evidence.—To investigate this problem cats were used as experimental animals. One superior cervical sympathetic ganglion was removed to sensitize the pupil to epinephrine. After recovery from this operation the horizontal diameter of the cats' pupils was measured in a darkened room under standard lighting conditions. The measurements were made when the cats faced a 300 watt electric light bulb at a distance of two meters. After training, it was possible to get consistent readings after a preliminary rest period of 15 minutes. The smallest diameters of the left and right pupils which could be obtained and the degree of retraction of the nictitating membranes were noted. Then 0.3 to 0.5 cc. of epinephrine 1 :1,000 (Burroughs and Wellcome) in 5 cc. of a physiologic saline solution was injected intraperitoneally and the size of the pupils measured at intervals of ten minutes, until they returned to the original or preinjection sizes. This usually occurred after 30 minutes. The same procedure was repeated two or three times with an interval of four or five days between observations. The results of the tests were strikingly uniform.

With this dosage of epinephrine there was usually no change in the size of the normal pupil; the sympathectomized pupil generally enlarged 0.5 to 1

Mm. The normal nictitating membrane usually was unaffected while the sensitized one showed slight retraction.

In 19 animals, in which one or both renal arteries were constricted by the method of Goldblatt, five showed a definite and lasting increase in the diameter

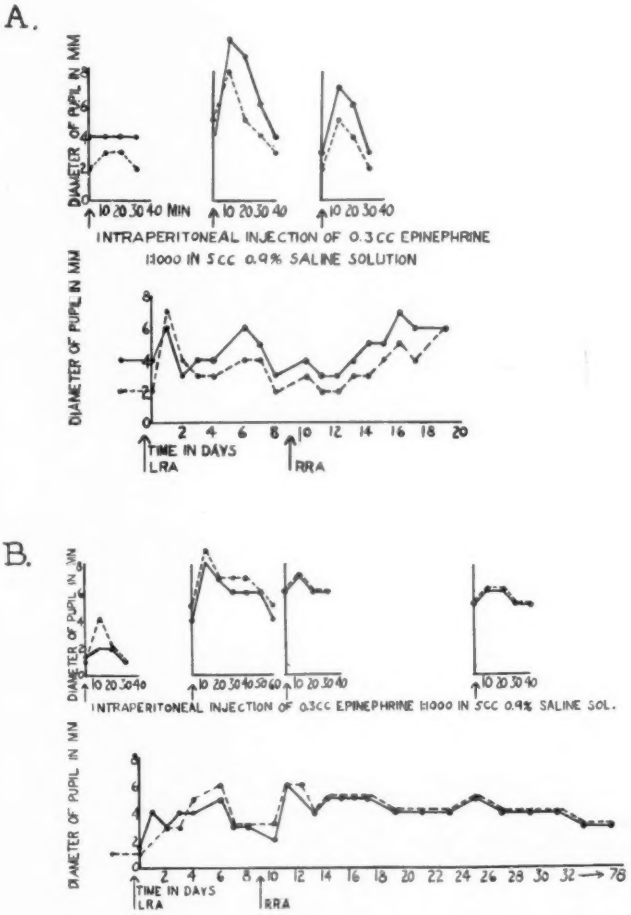
A.
DIAMETER OF PUPIL IN MM
10 20 30 40 MIN
INTRAPERITONEAL INJECTION OF 0.3 CC EPINEPHRINE
1:1000 IN 5 CC 0.9% SALINE SOLUTION
TIME IN DAYS
LRA
RRA
B.
INTRAPERITONEAL INJECTION OF 0.3CC EPINEPHRINE 1:1000 IN 5CC 0.9% SALINE SOL.

CHART 1.—Graphs A and B show the responsiveness of the pupils of two cats to exogenous epinephrine 0.3 cc. in 5 cc. N/saline given intraperitoneally and their transverse papillary diameters at various intervals after the application of Goldblatt clamps to their renal arteries. LRA and RRA indicate times of application of clamps to left and right renal arteries, respectively. Broken line for sympathectomized pupil, solid line for companion pupil.

of both pupils, the sympathectomized ones showing a relatively greater increase (Chart 1). In fact, in three of the cats the sympathectomized pupil became equal in size to the normal. In five other animals a transient increase in the sizes of both pupils was obtained. The remaining animals, some of which did not live more than a week, showed no change. In all instances, where a definite increase in the size of the pupil was secured, there was also an

increase in their responsiveness as evidenced by pupillary dilation to exogenous epinephrine. In four other cats, in which one kidney was removed and the other wrapped in silk, according to the method of Page (1939), there was a gradual increase in the size of the sympathectomized pupil and a moderate increase in response of this pupil to exogenous epinephrine. In one of the cats the sympathectomized pupil became larger than its companion pupil which also increased somewhat in size (Fig. 1). Both pupils in this animal were greatly sensitized to exogenous epinephrine. In general, it seems true that the degree of increased responsiveness to epinephrine goes hand in hand with the degree of increase in size of the pupil. The tone of the denervated nictitating membrane as evidenced by its retraction was increased following renal ischemia in over 60 per cent of the animals. It is not possible to judge accurately the tone of the companion nictitating membrane.

FIG. 1.—Photographs showing the pupils of two cats. A. Normal cat one week after removal of right superior sympathetic ganglion. B. Another cat three months after removal of right superior sympathetic ganglion, removal of one kidney and envelopment of other kidney in silk. Note in A right pupil smaller than left, in B right pupil actually larger than left.

It is realized that these experiments are incomplete in that no blood pressure readings are available. In chronic animals autopsy, however, revealed definite left ventricular hypertrophy which may be regarded as fair evidence of the existence of previous hypertension. Such animals had a moderate elevation of urea nitrogen (50 to 90 mg. %) but there was no correlation between the degree of nitrogen retention and the degree of change in the size or responsiveness of the pupils. It is to be noted that the removal of all renal tissue in the normal or hypertensive cat will, after two days, in itself, sometimes result in an enlargement of the sensitized pupil and in an increase in its responsiveness to exogenous epinephrine. It seems reasonable to consider on the basis of our experiments that the substance released from the ischemic kidney which increases the tone of the smooth musculature of the eye of an animal and makes it more responsive to epinephrine is also the pressor substance. Verney and Vogt (1938) report that in three out of seven hypertensive dogs there was a marked increase in their sensibility to epinephrine when blood pressure response was used as a criterion.

Our results are taken to indicate that in certain cats renal ischemia may lead to an increase in the tone of the smooth musculature of other structures as well as blood vessels. This effect on the eye musculature and possibly also on the blood vessels may result in a coincidental increase in their responsive-

ness to exogenous epinephrine. This is not construed as indicating that in certain animals hypertension is due to a sympathomimetic substance like epinephrine though epinephrine may play a rôle, for instance, in the hypertensive crises in cases of human hypertension. It also affords a basis for the belief that adrenal denervation in certain individuals may have a very definite influence on their nervous reactions.

The failure to get positive results in all animals is not explained. It is possible that an inadequate degree of renal ischemia was produced in some or it may be that animals like humans differ in their reactivity to stimuli affecting their smooth musculature.

Effect of Epinephrine and Adrenal Denervation on the Nervous System.—The effect of epinephrine on the isolated, spontaneously active ganglion cells of the Limulus heart cord is to increase the frequency and the magnitude of the ganglion cell response (Heinbecker, 1936). In experiments now in progress, the effect of an increase in the amount of circulating epinephrine on the activity of the central nervous system of the cat is being determined. Preliminary results demonstrate that such an increase of epinephrine results in a lowering of the threshold for the immediate cortical response to saphenous nerve stimulation and causes an augmentation in the size of this response to stimuli of a given strength. An increase in the general cortical activity is evidenced by an increase in the size of the cortical potentials.

During activity, the central nervous system must be influenced by the circulating epinephrine. In view of the results cited, it seems reasonable to assume that a diminution in the amount of circulating epinephrine, such as would be effected through adrenal denervation, would raise the threshold for the cortical response to afferent stimuli and diminish the size of the response to stimuli of a given value. Such effects would seem to afford a possible explanation of the raised threshold for discomfort and the lessened excitability of persons with hypertension on whom a splanchnic section has been carried out.

Clinical Effects of Splanchnic Nerve Section.—From our knowledge of the mechanism of the production of hypertension and of the associated effects in animals, certain inferences can be drawn as to what could be expected from splanchnic section in various stages of the disease in humans. Four case records to illustrate the actual results for comparison with those theoretically expected are presented.

Consider, first, the stage where the renal ischemia is brought about by functional narrowing of the renal vessels through nervous influences with no irreversible kidney damage. Splanchnic section should permit the renal blood flow to return to normal, the hypertension should be completely relieved. Such a stage is believed to be illustrated in Case Record 1:

Case Record 1.—I. D., white, female, age 20. Elevated blood pressure discovered during routine examination—only symptom, slight dyspnea on exertion. Father died of heart disease, mother living, has hypertension. Two brothers and one sister have hypertension. Blood pressure 180 to 160/110 to 105. Eyegrounds normal. Urea clearance 76 per cent. Urine normal. Heart not enlarged. After nembutal, blood pressure

130/90. In cold pressor test, blood pressure rose from 155/105 to 180/120. Bilateral splanchnic section, April, 1938. After operation, blood pressure dropped to 120/60 and remained there for eight months. Was married, January, 1939. Miscarriage after three months' pregnancy, August, 1939. In November, 1939, blood pressure 144/98; in March, 1940, blood pressure 165/110. Patient has slight dyspnea, is nervous and somewhat irritable.

Case Record 1 further demonstrates the detrimental influence of pregnancy on a patient with potentialities for the development of hypertension. Humoral influences released during pregnancy presumably again produced narrowing of the denervated renal vessels of the kidneys, and thereby initiated a disease process which, in our experience, is progressive, when not relieved by parturition. It illustrates a mechanism for the production of hypertension unassociated with the nervous control of the kidneys. Such a mechanism does not require the autonomic nervous system even for its initiation. Splanchnic section could not be expected to have any great influence on its progress.

Consider, next, a stage in which renal ischemia initiated through nervous influences has been present for some time and where the narrowing of the renal vessels is now held to be due to a self-perpetuating renal pressor substance. Damage to the renal parenchyma is so slight that tests such as the urea clearance do not reveal any damage to the excretory apparatus.

Splanchnic section, by the release of vasoconstrictor influences, might decrease the blood pressure to the same degree as could be accomplished by rest in bed and sedation. The effect of the operation would not be sufficient to permit the blood pressure to return to normal because the hypertension produced experimentally by the kidney pressor substances is unaffected by total sympathectomy, as Freeman and Page (1937) and others have shown. In this patient, denervation of the adrenals would be expected to relieve headaches, to lessen cardiac oppression and to effect a general quieting of the patient's nervousness, sleeplessness, *etc.* Such a stage is believed illustrated in Case Record 2.

Case Record 2.—C. G., white, female, age 43. Father died of dropsy; one sister has hypertension. Developed hypertension during her first, and only pregnancy at age of 28. Blood pressure as high as 205/140 before delivery. On discharge from Maternity Hospital, blood pressure 128/68. Three years later, blood pressure 160/100. Complained at that time of nervousness. Two years after this, N.P.N. 29 mg. per cent. P.S.P. 60 per cent in two hours. In 1938, entered hospital with blood pressure averaging 238/140. Complaints were constant headaches, 13 years; hysterical crying spells, two years; dizziness with fainting, five years; palpitation, ten years; insomnia, ten years. Eyegrounds showed moderate arteriolar sclerosis. Moderate cardiac enlargement. Laboratory tests showed urea clearance 84 per cent. Urea N. 12 mg. per cent. Highest specific gravity of urine attained 1.025. Bilateral splanchnic section, November, 1938. Blood pressure 17 months after operation, 230/130. Patient has been free of headaches and palpitation. She is less nervous. She tires more easily than before operation. Sleeps without sedatives. Considers operation has been definitely beneficial.

Consider, thirdly, a stage of the disease in which the functional constriction of the renal vessels has led to actual occlusive disease of these vessels. Retinal arteriolar sclerosis is definite. Renal function tests show a 50 per cent diminu-

tion in urea clearance. The blood pressure level is high with the diastolic pressure fixed at about 130 Mm.Hg. Symptoms associated with the hypertension are marked. Depression of the blood pressure on rest in bed is insignificant. Splanchnic section could not be expected to lower the blood pressure as the renal vessels are narrowed by pressor substances and occlusive disease to a point where any narrowing due to nervous influences is insignificant. Adrenal denervation would effect symptomatic improvement because of its influence on the nervous system and the elimination of blood pressure crises.

Case Record 3.—White, male, age 40, single. Known to have had high blood pressure for a year. Recently, has had marked dyspnea on exertion; fatigues easily; unable to work. Blood pressure 235/125. Heart definitely enlarged to left. Eyegrounds show minimal arteriolar sclerosis. E.C.G. shows definite myocardial damage. Urea clearance 50 per cent of normal. Highest specific gravity in urine concentration test 1.012. Urine shows plus albumin. Bilateral splanchnic section, March, 1938. Two years after operation, patient is working every day. Urine shows trace of albumin. Heart enlargement is less than before operation. Dyspnea less than before operation. No headaches. Blood pressure averages 215/135.

Consider, fourthly, a stage of the disease in which there is widespread occlusive disease of the renal vessels. There is diffuse retinal arteriolar sclerosis with extensive hemorrhage. The blood pressure is markedly elevated, with the diastolic fixed at 130 Mm.Hg. or over. It is not modified by rest in bed and sedation. Renal function tests show 25 per cent, or less, of the normal amounts of urea clearance. Symptoms from the hypertension are very marked.

Splanchnic section would not affect the blood pressure. Symptomatic relief could still be afforded. Progression of the disease would probably not be interfered with. Case Record 4 is taken to illustrate this stage.

Case Record 4.—H. B., white, female, age 47 Married and has two grown children. Father died of cardiorenal disease, mother of kidney trouble. Hypertension for five years. Complaints were headache, palpitation, cardiac asthma, dyspnea on exertion, nervousness. Blood pressure 260/140. No depression of blood pressure with rest in bed and sedation. Eyegrounds show moderate arteriolar sclerosis. Urine specific gravity 1.005. Urea clearance 15 per cent. N.P.N. 50 mg. per cent. Moderate enlargement of heart. Bilateral splanchnic section, February, 1938. One year later, patient free of headaches, palpitation less, fewer attacks of "cardiac" asthma, less nervous, living fairly normal life. Blood pressure 230/130. Urea clearance 23 per cent. One year and nine months after operation, patient free of headaches, slight edema of ankles which disappeared on low salt intake. Both patient and family satisfied with results of operation. Blood pressure 240/130. Urea clearance 12 per cent. Twenty-three months after operation, developed a cerebral hemorrhage—death within three days.

Surgery for Hypertension.—An analysis of our records thus shows a close correlation between the expected and the actual result of splanchnic section for hypertension. Splanchnic section can reduce blood pressure to normal where nervous influences are initiating the train of events which lead to a permanent stage of the disease process. It is believed that the only clinical evidence justifying the assumption that nervous influences still dominate the picture is to be found in the demonstration that the elevated systolic and diastolic pres-

sures will return to normal on rest and sedation. Splanchnic section will not lower blood pressure appreciably once the renal ischemia is effected by mechanisms not under nervous control. Symptomatic relief from "nervous" symptoms will be afforded in over 70 per cent of the cases. This, for reasons given, is considered an effect of the adrenal denervation. It is secured regardless of the effect on blood pressure. Evidence has not yet been accumulated for sufficiently long periods on a large enough number of cases to warrant any statement as to the influence of splanchnic section on the progress of the disease.

In the author's opinion, the rôle for the surgeon in the problem of hypertension is to determine whether or not and in what types of cases renal-adrenal denervation performed at the very onset of the disease, before there is any fixed blood pressure elevation, will effect a permanent drop in blood pressure and restore renal circulation to normal. He will, thus, solve the question as to what part the nervous system plays in the initiation of the disease. He will doubtless also secure evidence as to the frequency with which causes other than nervous ones are responsible for the initiation of the hypertensive state. Only when such evidence is available will it be possible to select the cases suitable for splanchnic section.

SUMMARY AND CONCLUSIONS

Essential hypertension results when there is narrowing of peripheral arterioles with a maintained cardiac output. The vascular narrowing, presumably, is effected by a renal pressor substance released during a state of renal asphyxia.

It is believed that the initiation of the renal arteriolar narrowing necessary to bring about the renal asphyxia may be effected by nervous or humoral influences.

Regardless of the manner of its initiation, the process can become self-perpetuating. Neither nervous nor endocrine influences need, thereafter, play an essential rôle.

It is regarded as highly probable that hypertension occurs particularly in persons whose blood vessels are so constituted that they respond hyperdynamically to vasopressor influences. If such pressor influences are present in abnormal amounts, even normal renal blood vessels may constrict sufficiently to initiate renal ischemia.

Experimental and clinical evidence is cited to show that continued functional narrowing of blood vessels leads to occlusive narrowing. The degenerative changes characteristic of the occlusive disease are presumed to follow interference with the function of the vasa vasorum.

Splanchnic section may be expected to relieve renal ischemia initiated by vasoconstrictor influences if the renal ischemia has not become self-perpetuating.

Evidence that epinephrine lowers the threshold for excitatory influences on

the nervous system and increases the magnitude of the cortical response to identical peripheral stimuli is presented.

The symptomatic relief afforded by splanchnic section, in cases where there is no drop in blood pressure, is considered due to adrenal denervation.

Experimental evidence that a substance produced as a consequence of renal ischemia may increase, in certain animals, the tone of the smooth muscle of the iris and nictitating membrane is reported. Under such circumstances the effect of exogenous epinephrine on these structures is also enhanced.

Typical case records showing the effect of splanchnic section at various stages of hypertensive disease are presented.

A rôle for the surgeon in the solution of the problem of essential hypertension is to determine the number and types of cases in which nervous influences set into activity the mechanism by which hypertension is initiated. This can be done only if cases are treated in their initial stage.

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FACTORS INFLUENCING THE PROGNOSIS IN OSTEOGENIC SARCOMA*

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ANYONE who has had an opportunity of following a considerable number of cases of osteogenic sarcoma over a period of years must admit that the results of treatment are not encouraging. The clinician is baffled by the fact that, while approximately four-fifths of all cases terminate fatally in less than five years, an explanation of why the other one-fifth survive is still lacking.

That a number of factors combine to influence the prognosis seems obvious. We feel that the resultant of all these factors determines, in a given case, whether the patient will succumb or survive.

With a view toward attempting to evaluate these factors, we have recently studied a group of 217 cases of osteogenic sarcoma observed at the Memorial Hospital. Included are 53 cases without microscopic confirmation, and, in addition, an indeterminate group of four cases (see Table IX). Excluding these 57 cases, we have a determinate group of 160 cases, all with microscopic confirmation. Of these, 121 are listed as failures, 117 having died of sarcoma; and four others with the disease still present being lost to follow-up. There remain 35 cases free of disease five years after treatment, which, based on the determinate group, gives a five-year survival rate of 22 per cent.

Among the factors we have considered are: Age, sex, interval elapsing between onset of symptoms and amputation of limb; anatomic location of tumor; biopsy; histologic grading of tumor; and nature of treatment employed.

Age Incidence.—The material has been divided into what seems to be significant age-groups, that is, each embracing a decade (Table I). While no age-group is immune, the peak incidence occurs in late adolescence. The most significant inferences concern patients in the first decade. Here, regardless of duration, symptoms or histologic pattern, the prognosis is exceedingly bad.[1] In patients over 40 the prognosis is nearly as bad. There were 46 patients from 40 to 70 years of age. Of these, six or 13 per cent survived. Included were nine with Paget's disease on which osteogenic sarcoma was secondarily engrafted. The ages of the latter ranged from 43 to 63. Of these, but two survived, one an ilium case and the other a femur.

Sex Distribution.—Of the 160 cases, 100 or 60 per cent were males.

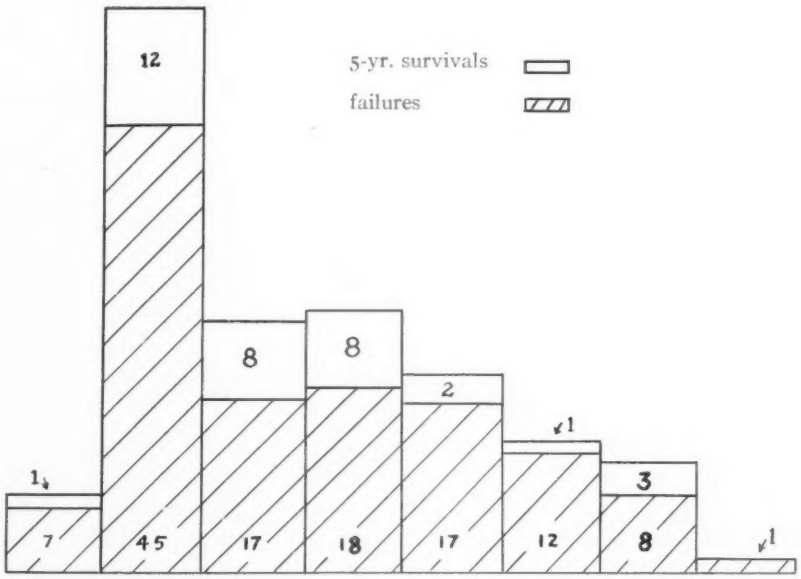
* Presented by title before the American Surgical Association, St. Louis, Mo., May 1, 2, 3, 1940.

TABLE I

AGE INCIDENCE

Memorial Hospital Series, 1917–1935

160 Cases, Proven Histologically—35 Five-Year Survivals



Age	0–10	11–20	21–30	31–40	41–50	51–60	61–70	73
Survivals	13%	21%	32%	31%	11%	8%	27%	0%

However, the survival rate of the females was 28 per cent as compared with 18 per cent in the males. We are unable to account for this apparently better prognosis in the female (Table II).

TABLE II

SEX DISTRIBUTION

	Total	Dead of Disease	5-Year Survivals
Male.....	100	82	18
Female.....	60	43	17
Totals.....	160	125	35

Pathologic Fracture.—This complication, which occurred in 15 cases, or approximately 10 per cent of the total number, might be expected to have a serious influence on the prognosis. In an earlier communication,[2] 21 per cent of 122 cases had this complication; and the duration of life averaged ten months less than in the cases without fracture. In this study, we found that in the fatal cases the duration of life was halved. One would expect, how-

ever, that cases with fracture would show a survival percentage much lower than the cases without fracture. Early pathologic fracture is seen most often in rapidly growing, histologically malignant tumors. The factor of fracture itself, by producing intratumoral hemorrhage and favoring the liberation of cell emboli in the manner in which fat emboli are discharged after uncomplicated fractures, would seem to be of importance. Yet, of the 15 cases, three survived, giving a rate of 20 per cent, which is only slightly lower than that for the series as a whole (22 per cent).

Interval Elapsing Between Onset of Symptoms and Amputation.—A comparative study of the failures and successes shows that there was an interval of one year or more in 18 per cent of the patients that died, and in 22 per cent of those that survived. This variation is not significant. It does seem important to consider the causes of this procrastination. While in some the mildness of the symptoms was apparently responsible, in the majority it may be attributed to failure to make a correct diagnosis, resulting in a loss of time while improper treatment was being administered. Failure to make roentgenologic examination of a painful extremity is the commonest error, and sometimes an inadequate examination was responsible. The roentgenograms should include a considerable area proximal to the point of pain, and views in several planes and stereoscopically are advisable.

In the group that died, the 37 per cent who came for early treatment all had highly malignant tumors. A large majority of those in the first decade and in the first half of the second decade also had tumors of high malignancy. The patients who delayed for from three to 12 months include many who had relatively low-grade or peripherally situated tumors: yet these tumors because of the delay, had had time to metastasize. It is believed that earlier treatment would have cured some of these patients.

In the five-year survivals, the longest interval between onset and treatment occurred in the case of a female, age 29, with a low-grade chondrosarcoma expanding the anterior portion of the left fifth rib. She waited for seven years after first noticing the swelling in this rib before seeking medical advice. Another patient, who waited for five years, had a medullary chondrosarcoma involving the lower two-thirds of the left humerus—a slowly growing but definitely malignant tumor.

Anatomic Location of Tumor.—Our study discloses that the femur, especially the lower third, is the most frequent site, with the upper ends of the tibia, the humerus, and the fibula, ranging in order. In the tubular bones, osteogenic sarcoma occurs most frequently in the metaphyseal region, tending to invade both the epiphysis and diaphysis secondarily. That it should occur most readily in the metaphyseal regions of greatest growth is not surprising.

The peripheral sites of orgin apparently offer a better prognosis than do those more centrally located; thus, osteogenic sarcoma of the bones of the forearm and of the feet gives a better than 50 per cent prognosis. Also notable is the femur; no survivals occurred in cases primary in the middle or upper third, although some cases surviving five years with a primary site in

the lower third of the bone did have extension more than a third of the way up the shaft.

The mortality for osteogenic sarcoma located in the flat bones and the

TABLE III

PRIMARY SITE IN 160, HISTOLOGICALLY PROVEN, CASES OF OSTEOGENIC SARCOMA

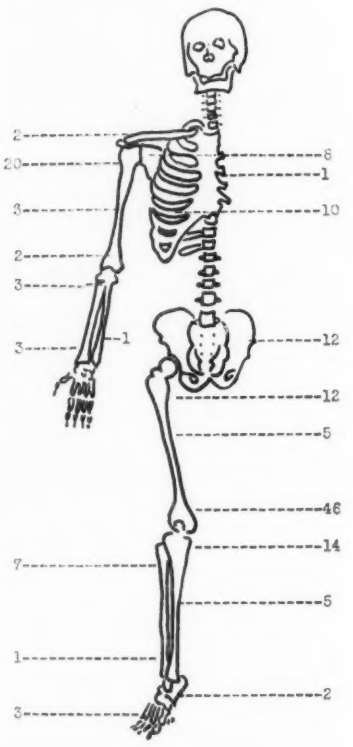
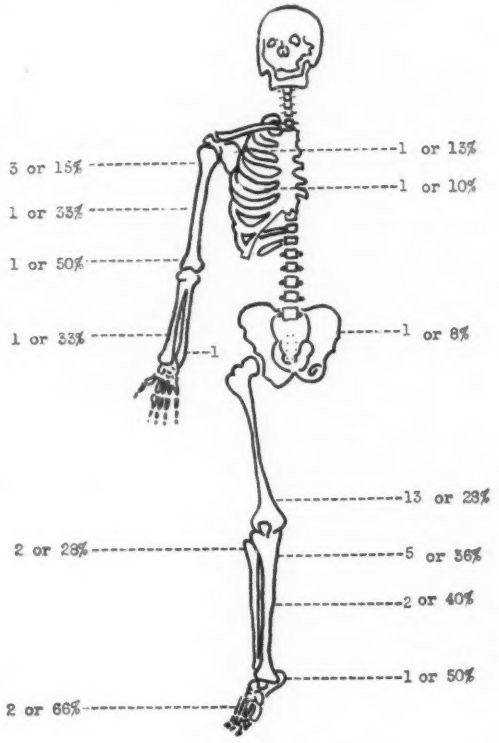


TABLE IV

PRIMARY SITE IN 35 PATIENTS WHO SURVIVED FIVE YEARS FROM TIME OF TREATMENT



ribs is worse even than that for osteogenic sarcoma in the extremities; in this series one of each survives (Tables III and IV).

Biopsy.—Aspiration biopsy, in our hands, has proven an excellent method for establishing the diagnosis, and has been successful in over three-fourths of the cases in which it has been attempted.

The use of open surgical biopsy, despite the inherent theoretic dangers, has a definite place. In our series, 58 such biopsies were performed—42 in the unsuccessful and 16 in the successful groups. The inadvisability of resorting to radical surgery without a pathologic confirmation of the diagnosis is well known. In selected cases, properly performed biopsies were not followed by complications, and even when amputation had to be performed in the course of the next week or two, there was no apparent increase in the mortality rate. Fungation and ulceration have followed improperly per-

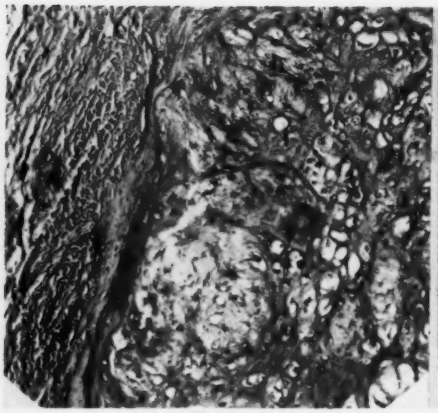


FIG. 1

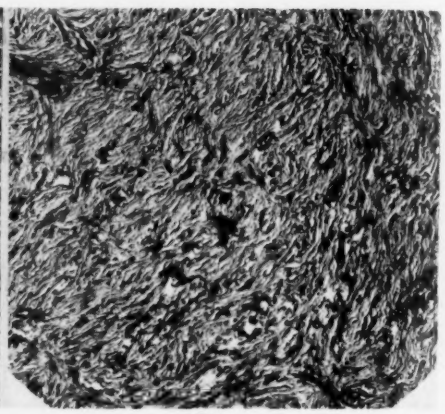


FIG. 2

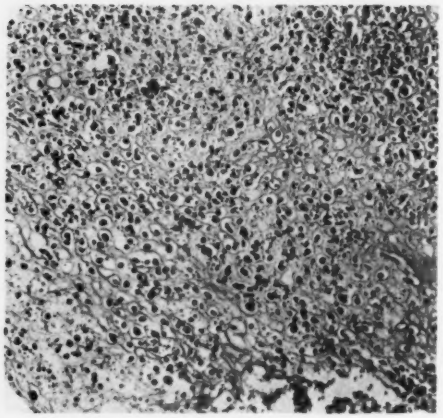


FIG. 3

FIG. 1.—A low-grade chondrosarcoma, showing well-defined demarcation between cartilage and fibrous capsulae. (×45)

FIG. 2.—A low-grade periosteal fibrosarcoma, showing relative uniformity of cell, moderately well-defined structure of fiber bundles, and poor vascularity. (×45)

FIG. 3.—An average chondroscarcoma in which cells are numerous. Nuclei tend to be large and variable in shape and staining. Intercullular substance is moderate in amount. (×45)

FIG. 4.—A cellular spindle cell osteogenic sarcoma of medullary origin and average malignancy. (×45)

FIG. 5.—A high-grade osteogenic sarcoma, showing cell pleomorphism, telangiectasis, and a mucoid stroma. (×120)

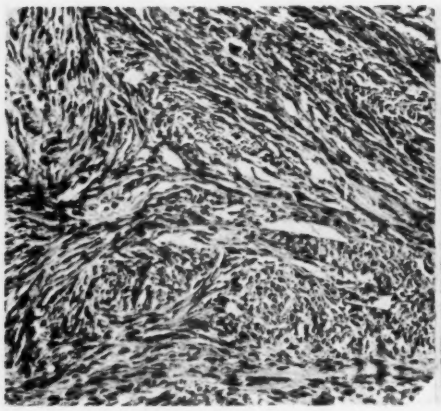


FIG. 4

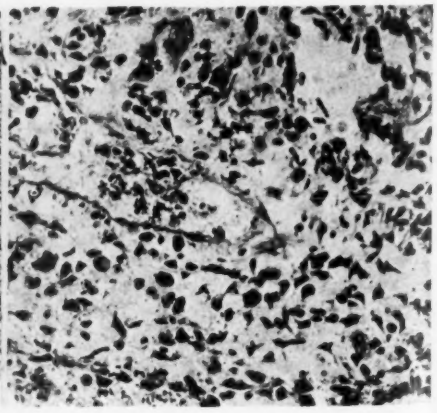


FIG. 5

formed biopsies. Probably, the procedure should be, to reserve open biopsy for cases in which the aspiration method has failed. If an immediate amputation is decided upon, the biopsy should be performed, using a tourniquet so that the amputation can be carried out at once if the pathologist's report on the frozen section or smear is that of sarcoma.

These open biopsy wounds should invariably be closed without drainage and never packed. Failure to observe this precaution has resulted in fungation of the wound, secondary infection, and alteration of the growth rate, thus precluding adequate later treatment.

Pathology.—The grade of malignancy encountered must be determined by an evaluation of a number of factors. The gross pathologic picture is important, for it shows the presence or absence of invasion into the epiphysis; whether the tumor is medullary, periosteal or both in its extent; and whether the adjacent soft parts are invaded. Extension of tumor tissue for a considerable distance up the narrow cavity, invasion of the femoral or axillary vein, extensive infiltration of overlying soft parts, tissue of a telangiectatic character, all are of extremely unfavorable significance; conversely, their absence is more favorable.

Microscopically, the grade of malignancy is demonstrable by a uniformity or pleomorphism of the cell type, and we feel that in a given case, the most highly malignant area seen under the microscope should determine the grade. That such grading of the tumor is of importance in the outcome of the case is seen in Table V, which indicates a survival rate of 40 per cent for low-, 16 per cent for average-, and 15 per cent for high-grade tumors. The fact that the average- and the high-grade tumors have an almost identical survival rate might indicate that histologic criteria of the two groups are less distinct than are those of tumors of low-grade malignancy.

TABLE V

OSTEOGENIC SARCOMA

Pathology

(1) Patients dead of disease		125
a. Tumor of low-grade malignancy	21 or 17%	
b. Tumor of average-grade malignancy	82 or 65%	
c. Tumor of high-grade malignancy	22 or 18%	
Total	125	
(2) Patients surviving five years		35
a. Tumor of low-grade malignancy	15 or 43%	
b. Tumor of average-grade malignancy	16 or 46%	
c. Tumor of high-grade malignancy	4 or 11%	
Total	35	

In other words, of 36 cases with tumors of low-grade malignancy, 40 per cent survived five years; of 98 with tumors of average-grade malignancy, 16 per cent survived five years; and of 26 with highly malignant tumors, 15 per cent survived five years.

Methods of Treatment.—Amputation: Amputation has been, and still is, the most generally accepted method of treating operable osteogenic sarcoma. There are, however, exceptional cases in which less radical surgical measures may be indicated. That amputation should be performed at once and without recourse to radiation is debatable.

Of 92 cases subjected to amputation, there were three operative deaths; in each instance the operation was carried out at another hospital.

Of the remaining 89 cases, 60 died of the disease and 29 lived for five years or more, a survival rate of 32 per cent.

Analyzing this group still further we find the following: Of 17 cases treated by amputation alone, five, or 29 per cent, survived five years; of 21 cases treated by amputation after preliminary surgery, seven, or 33 per cent, survived five years; of 41 cases treated by amputation after radiation, 14, or 34 per cent, survived five years.

Table VI shows the deaths and survivals in those cases amputated during the first six months, in the second six months, and one year or more after the onset of symptoms.

TABLE VI

ANALYSIS OF RESULTS IN 89 CASES OF OSTEOGENIC SARCOMA SUBJECTED TO AMPUTATION

					*1 to 6 Months**		*7 to 12 Months*		*13 Months Plus*	
	Total	Dead of Disease	5-Year Survival	Per Cent	Dead of Disease	5-Year Survival	Dead of Disease	5-Year Survival	Dead of Disease	5-Year Survival
Total subjected to amputation	89	60	29	32	35	7	15	9	10	13
Amputation only	17	12	5	29	4	3	6	1	2	1
Amputation after preliminary conservative surgery	21	14	7	33	10	3	2	2	2	2
Amputation after radiation	41	27	14	34	18	1	5	5	4	8
Amputation after radiation and other surgery	10	7	3	30	3	0	2	1	2	2

*Interval of time in each case refers to months elapsing between first appearance of tumor and date of amputation.

In general, this table tends to support Ferguson's[5] assertion, based on a somewhat similar survey of cases on file with the Bone Sarcoma Registry, that the cases in which amputation was performed *after* a lapse of six months from the appearance of the first symptom showed a higher percentage of five-year survivals than did those in which amputation was performed during the first six months. In our opinion, however, it has by no means been established that delayed amputation was responsible for the better results. The question naturally arises: Why were some amputations performed at once and why were some delayed? We offer the following answer: Those cases amputated early had much more rapidly growing, symptom-producing tumors, and represented tumors of a higher degree of malignancy as shown by the histologic grading. For example: Forty-two cases were amputated within six

months of onset of symptoms. Only three, or 7 per cent, were low-grade tumors, and 21 per cent were highly malignant. The survival rate was 16 per cent for this group. Cases amputated between six and 12 months after onset showed eight out of 24, or 33 per cent, low-grade tumors; the group as a whole had a survival rate of 39 per cent; and a 50 per cent survival in the low-grade tumors. Cases in which amputation was delayed for more than a year (23) included eight, or 35 per cent, low-grade osteogenic sarcomata. Here the survival rate was 56 per cent for the whole group; and 62 per cent for the low-grade tumors. *The proportion of lower degrees of malignancy, thus, bears some ratio to the survival rate.*

We believe that delay, of itself, is undesirable, and, if generally practiced, will result in fewer survivals. If, for any reason, a delay is enforced upon the surgeon, then heavy radiation with roentgenotherapy should be administered in the interval. Less harmful effects of procrastination are apt to follow this practice. We have not observed, except in cases heavily radiated, any rhythmic periods of activity and quiescence, as described by Ferguson. Nor do we believe that excision is useful in "creating a proper time to amputate." Excision should be reserved for exceptional cases both as to anatomic considerations and low-grade malignancy.

If, when the patient is first seen, tumor cells are assumed to be in the circulating blood, we doubt that radiation, resection or amputation can exert any inhibitory action upon them. This highly desirable effect, we believe, must await a more efficient systemic agent than has as yet been discovered. The effect of bacterial products on certain malignant tumors in animals seems a possible lead in this direction.

Level of Amputation.—The dictum that amputation should be carried out at least at the next higher joint and never through the bone involved is, in our opinion, without support. While admitting that, in most instances, it is desirable to avoid transecting the affected bone, we do not feel that a hip-joint disarticulation should be recommended for every osteogenic sarcoma of the lower end of the femur. The results would seem to show that hip-joint disarticulation is not more effective than subtrochanteric amputation where judgment is used in the selection of cases for the less radical procedure. We believe it significant that of the 29 five-year survivals treated by amputation, 15, or more than 50 per cent, were amputated through the bone involved, four were disarticulated through the proximal joint, and ten were amputated through the proximal bone (including interscapulothoracic amputations). Furthermore, there were 43 femur cases treated by amputation, of which four had hip-joint disarticulation, with no survivals. Of the remaining 39 in which high thigh amputation was performed, there were 12 survivals (Table VII).

Resection.—Resection was attempted in 17 cases. There were only two five-year survivals, *i.e.*, a rib and a tibia. Resection always carries the risk of a recurrence which calls for further operation and, perhaps, late amputation.

TABLE VII

SITE OF AMPUTATION

	No. of Cases	Failures	5-Year Survivals
Submitted to amputation	92		
Suitable for end-result study	89		
Amputated through bone involved	42	27 or 65%	15 or 35%
Amputated through *joint* proximal to bone involved	19	15 or 78%	4 or 21%
Amputated through *bone* proximal to bone involved*	28	18 or 65%	10 or 36%
Totals	89	60 or 66%	29 or 33%

* Includes interscapulothoracic disarticulation.

Radiation.—Radiation alone was employed in 35 cases, with 32 deaths and three five-year survivals. In the latter, the tumor was located in the tibia, humerus and ilium. In two cases, the tumor was superficially located without much soft-part tissue between it and the source of radiation. All received heavy radiation. In one case, interstitial radiation by means of removable radon needles was administered in addition to external radiation with the radium element pack. It should be especially noted that in each instance the tumor was of a low-grade, slowly growing type.

Radiation as a preoperative measure will often alleviate pain and sometimes cause a diminution in the size of the tumor, thus rendering it operable. Radiation may hold the disease in check while the patient and his family are being convinced of the necessity for amputation.

One must conclude that preoperative radiation is worthy of a continued trial from the fact that of 41 cases in this series treated by amputation after radiation, 34 per cent lived for five years—a slightly higher percentage than was obtained in the groups treated by amputation alone or amputation following preliminary surgery.

In the following three cases the patients survived five years following radiation therapy alone:

Case 1.—B. S. R. No. 1453: G. R., female, age 36. In February, 1929, a swelling was noted on the anterior aspect of the proximal third of the left arm. This slowly increased in size, and an incisional biopsy was performed 11 months later. Four months thereafter, the patient was examined by Doctor Ewing, at the Memorial Hospital, who made a diagnosis of periosteal fibrosarcoma on the biopsied tissue. Roentgenologic examination revealed no bone destruction. During the course of 20 days, the patient received a tissue dose of 4,700 r. to the tumor (one-third by external radiation with the 4 Gm. element pack, and two-thirds with platinum filtered removal needles). At the present time, nearly ten years later, the arm function is normal, although there is marked fibrosis at the site of the tumor.

Case 2.—H. F., male, age 21, in June, 1931, struck his right shin a sharp blow against the rim of a barrel. A hematoma developed which did not absorb. Roentgenologic examination revealed an expansile, central, cystic area of destruction in the lower third of the tibia. Doctor Ewing examined a biopsy section and reported it to be a low-grade fibrosarcoma of medullary origin. A tissue dose of 900 r. (200 K.V.) was administered to the upper and lower half of tumor, which had shown no further increase in size. Similar smaller cystic defects have been noted in other tubular bones.

Case 3.—B. S. R. No. 1517: S. G., male, age 59, first noticed pain in the region of the right hip in February, 1930. This was followed six months later by weakness of the right leg on standing, and a swelling in the groin one year later. Nearly three years after the onset of disability, a physician was consulted who referred the patient to the Memorial Hospital. Roentgenologic examination revealed a huge, destructive, osteolytic, expansile process of the right ilium. There was also evidence of Paget's disease in the femora, tibiae and humeri. A punch-biopsy section from the ilium was examined and pronounced an osteogenic sarcoma of spindle and giant cell type. Between January 31 and May 1, 1931, a tissue dose of 3,200 r. (200 K.V.) was administered. There was progressive flattening of the acetabulum but 18 months later the tumor showed complete recalcification which remained unchanged until the patient's death in January, 1940. One year previously, the radiated skin in the groin had become ulcerated, but the patient refused further hospitalization and died as an indirect result of this ulceration but without evidence of active sarcoma (Table VIII).

Toxin Treatment.—(The mixed toxins of erysipelas and *Bacillus prodigiosus*, or Coley's toxins.) The toxins were administered in 91 cases in this series, of which 20 survived. The part they played in the five-year survivals is very difficult to evaluate. They seem definitely indicated during the postoperative period in young individuals and, in general, in combination wth amputation and possibly preoperative radiation in highly malignant tumors. The recent experimental studies of Schwartzman and his associates,[6] Andervent, Fogg, Jacobi and others, on the effect of bacterial products on malignant tumors, are confirmation of the fact brought out many years ago by Fehleisen,[8] W. B. Coley,[9] Lassar[10] and Spronck[11] that bacterial products sometimes exert a profound effect upon malignant tumors.

TABLE VIII

METHODS OF TREATMENT OF 144 CASES OF OSTEOGENIC SARCOMA*

		1 to 6 Months		*6 to 12 Months*		*13 Months Plus*	
	Total	Dead of Disease	5-Year Survival	Dead of Disease	5-Year Survival	Dead of Disease	5-Year Survival
Amputation only	17	12	5	4	3	6	1	2	1
Amputation following biopsy	15	12	3	9	2	2	1	1	
Amputation following radiation	41	27	14	18	1	5	5	4	8
Amputation following resection	4	1	3	1			1		2
Amputation following curettage	2	1	1		1			1	
Amputation following radiation and resection	6	4	2	2		1		1	2
Amputation following curettage and radiation	4	3	1	1		1	1	1	
Resection only	17	15	2	6		4		5	2
Radiation only	35	32	3	22	1	7		3	2
Curettage and radiation	3	2	1	2				1	
Totals	144	109	35	65	8	26	9	19	17

* Of the entire group of 160 cases, 16 were unsuitable for this analysis, *viz.*: Three died following operation elsewhere; nine had only palliative treatment following metastases; and four were too far advanced for treatment.

Further experimental work along the lines of treatment by bacterial products is, undoubtedly, necessary. While for osteogenic sarcoma we are not prepared to claim for the toxins any well-established therapeutic effect in the prevention of metastasis, we still feel that their use following amputation is worth while; particularly is this true of the highly malignant anaplastic types which have an exceedingly unfavorable prognosis by amputation alone.

An evaluation of the effect of the various methods of treatment and of the histologic character of the tumor present is best approached by a consideration of the problems raised in the individual case. In the following ten cases, we have tried to weigh carefully all the favorable and unfavorable features in an attempt to explain why the patient did or did not survive.

Case 4.—G. M., male, age 16, noticed a swelling in the midshin ten days after a direct trauma. This diminished but never entirely disappeared, and because of increasing local pain, the patient appeared at the Memorial Hospital nine months later. The pain was relieved by a moderate dose of 200 K.V. roentgen ray; amputation was performed four months after admission.

In this patient's favor are the following: (1) That he is in later adolescence; (2) that a relatively peripheral bone is involved; and (3) that the tumor responded, at least somewhat, to radiation, as indicated by relief of pain. On the other hand, there was a 13 months' delay between the onset and the amputation. While the specimen shows a tumor partially cartilaginous, it invades the epiphysis and the soft tissue. Microscopically, there are cartilaginous areas showing radiation effect, and also areas of highly malignant sarcoma. The patient has had no recurrence in ten years.

Case 5.—M. B., female, age 15, had pain and swelling of the right knee over a period of two months. Roentgenologic examination showed an osteogenic sarcoma, partially sclerosing. Following two negative aspiration biopsies, a formal biopsy and immediate amputation were performed, after which a course of Coley's toxins was given. The patient has remained well for six years.

Although microscopic studies showed a highly malignant spindle and giant cell tumor, osteolytic in many areas, and despite the patient's age, prompt and decisive treatment resulted in a survival beyond the five-year period.

Case 6.—G. K., male, age 31, noticed pain in the right knee for one and a half months before consulting his local doctor. The latter treated him with ointments, massage, and ultraviolet light for three months before sending him to the clinic. An immediate high thigh amputation was performed without a preliminary biopsy, following which a postoperative course of toxin treatment was instituted. Pulmonary metastasis appeared eight months later. Pathologically, this tumor of the lower femur was a low-grade chondrosarcoma. Its location, and the age of the patient were favorable factors but the early faulty treatment probably aided materially in disseminating the disease.

Case 7.—J. H., female, age nine, was admitted two months after onset of pain in the midthird of the right arm. The lesion, as seen in the roentgenograms, was confirmed by aspiration biopsy. Despite a shoulder-joint disarticulation and strenuous course of Coley's toxins, metastases appeared, first in the left tibia, then in the femur, and finally in the skull and lungs. The tumor was a highly malignant chondrosarcoma, probably of periosteal origin. Here, despite the relatively favorable site and the prompt and strenuous therapy, the relative youth of the patient and the malignancy of the tumor determined the fatal outcome.

Case 8.—R. B., female, age 16, complained of pain and rapid enlargement of the right upper arm over a period of two months. Moderate radiation and a course of toxins were administered for two months without visible effect on the tumor. A complete fracture occurred through the tumor and a disarticulation of the humerus was performed.

Pulmonary metastases appeared three months later. Pathologically, this tumor was medullary, subperiosteal, and had invaded the adjacent soft parts quite extensively—a factor which, with delay in amputation and the presence of a pathologic fracture, strongly influenced the outcome.

Case 9.—J. L., male, age 23, noticed pain and swelling one day after a light blow just below the knee. The patient came to the Memorial Hospital for treatment within the next four or six weeks. No biopsy was taken, but heavy dosage of gamma radiation was carried out for three months, followed by a midthigh amputation and a course of toxins. Pulmonary metastases appeared one month later. The gross specimen showed a tumor filling the marrow cavity, invading the epiphysis, and even elevating the joint cartilage; there was also marked invasion of the adjacent soft parts. Microscopically, the tumor showed much calcification, and many large spindle and giant cells indicative of a high-grade of malignancy. Despite the favorable site and the prompt medical consultation, the disease had already spread elsewhere by the time that the leg was removed. Perhaps the delay incident to the preoperative radiation lost for this patient his chance of a cure.

Case 10.—J. S., male, age 12, had had a tonsillectomy performed because of pains about the left knee. Four months later, a roentgenogram was taken and the patient was kept under observation for another two months. At the end of this time, a swelling appeared. An aspiration biopsy yielded a diagnosis of osteogenic sarcoma, and the patient was referred to the Memorial Hospital for treatment (eight months after onset). A ten-day course of high voltage roentgenotherapy was followed immediately by a subtrochanteric amputation and a course of toxins. Examination of the gross specimen showed a sclerosing tumor, cystic and hemorrhagic where it had elevated and invaded the periosteum, and calcified where it had extended along the marrow cavity, which was involved for a distance of 18 cm.

TABLE IX

END-RESULTS IN OSTEOGENIC SARCOMA

Memorial Hospital Series, 1917–1934 Inclusive		No. of Cases
1. Clinical diagnosis (exclusive of maxilla and mandible)		217
2. Without histologic verification of diagnosis		53
3. With histologic verification (summarized for this study)		164
a. Indeterminate Group:		
(1) Dead of other causes in less than 5 years, without recurrence	3	
(2) Lost to follow-up, without recurrence	1	4
		160
b. Determinate Group:		
(1) Failures:		
(a) Dead of sarcoma	121	
(b) Lost to follow-up, with disease	4	125
(2) Successes: Free of disease 5 years or more after treatment		35
4. Five-year survival-rate (determinate group)		22%

In this case, many factors are against survival, especially the eight months of expectant treatment in the presence of a rapidly growing, highly malignant osteogenic sarcoma; the youth of the patient, and the site of the tumor, i.e., the middle third of the femur. Metastases became apparent one month following the amputation.

Case 11.—This case represents an osteogenic sarcoma developing in Paget's disease. A male, age 63, complained of pain and stiffness about the left knee over a period of nine months. A huge tumor had developed. No treatment could be instituted, and at autopsy three months later, other osteogenic sarcomata, either metastatic or other primaries, were found in the right humerus and the right ilium.

TABLE X

SUMMARY OF FIVE-YEAR SURVIVALS OF OSTEOGENIC SARCOMA

Memorial Hospital Series, 1917–1934 Inclusive

No.	Year	Nm.	B. S. R. No.	Sex	Age	Bone	Interval* (Mos.)	Path. Group	Surgery	Radiation	Toxins	Survival Yrs.	Survival Mos.	
1	1918	B. M.	168	F.	33	Femur	72	II	Amputation	x		13	8	
2	1918	K. F.	373	F.	29	Rib	48	I	Resection	x	x	17	10	
3	1919	H. S.	172	M.	19	Femur	11	I	Amputation	x	x	19		
4	1920	L. O.	357	F.	31	Humerus	12	II	Amputation	x		11		
5	1921	I. R.	156	M.	12	Humerus	17	II	Disarticulation	x		11	9†	
6	1921	J. C.	177	M.	15	Tibia	4	I	Amputation			17	9	
7	1921	I. D.	365	F.	21	Femur	29	II	Amputation	x		10	5	
8	1923	R. M.	833	F.	8	Tibia	24	I	2 resections and amp.	x	x	14		
9	1925	C. C.	1352	F.	34	Humerus	7	I	Disarticulation	x	x	14	7	
10	1925	H. N.	921	M.	16	Fibula	1	III	2 resections and amp.	x	x	9	9	
11	1926	I. T.	1437	F.	63	Femur	16	I	Amputation	x		5	3†	(Paget)
12	1928	T. P.	1117	F.	37	Femur	13	II	Amputation	x	x	10	7	
13	1928	J. M.		M.	38	Tibia	48	II	Resection and radon needles		x	8	9	
14	1929	I. S.	1773	M.	47	Tibia	19	I	Resection and amp.	x	x	9	7	
15	1929	G. M.	1444	M.	16	Tibia	13	II	Amputation	x		5		
16	1929	G. R.	1453	F.	36	Humerus	11	I		radon needles		9	4	
17	1929	W. H.	1042	M.	19	Femur	2	II	Amputation		x	10	5	
18	1929	W.	1493	F.	34	Metatarsal	8	II	Resection and amp.			7	10	
19	1929	T. S.		F.	19	Tibia	47	II	Amputation	x	x	5	7	
20	1930	D. W.		F.	17	Femur	18	II	Amputation	x	x	9	5	
21	1930	S. K.	1941	M.	62	Femur	7	III	Amputation	x	x	9	2†	
22	1930	S. G.	1517	M.	59	Ilium	36	II		x		7†		(Paget)
23	1930	A. S.		F.	24	Ulna	8	III	Amputation			9	2	
24	1930	J. S.	1306	M.	65	Metatarsal	9	I	Amputation	x		8	7	
25	1931	H. F.		M.	21	Tibia	3	I		x		8	9	
26	1932	B. S.	1861	M.	43	Femur	31	I	Amputation		x	5	7	
27	1932	D. B.	1441	F.	15	Os calcis	4	III	Amputation		x	7	3	
28	1932	S. H.		M.	17	Ulna	3	I	Amputation			7	7	
29	1933	S. G.		M.	35	Scapula	35	I	Resection	x		5		
30	1933	L. B.	1769	M.	29	Fibula	20	I	2 resections and amp. Partial pneumonectomy for metas. 6 yrs. later		x	5	4	
31	1933	C. T.	1774	F.	34	Humerus	3	II	Curettage and disarticulation		x	6		
32	1934	M. B.	1767	F.	15	Femur	2	II	Amputation	x	x	5	9	
33	1934	A. L.	2065	M.	21	Femur	5	I	Local exc. and amp.	x	x	5		
34	1934	D. G.	1858	M.	16	Femur	5	II	Amputation		x	5		
35	1934	E. B.	2069	F.	6	Femur	6	II	Curettage and amp.	x	x	5		

* Interval elapsing between appearance of tumor and treatment, expressed in months.
† Patients dead of other causes after five years, without disease.

In the following five cases the patients lived for five years or more and then succumbed to the disease:

Case 12.—B.S.R. No. 100: E. P., female, age 23, first noticed a slowly growing tumor in the lower third of the right femur in December, 1915. This was curetted 13 months later, and about 1,000 r. by contact radium was administered. Six months later a midthigh amputation was performed. The specimen proved to be a Grade I periosteal fibrosarcoma. No evidence of a recurrence of the disease was noted until 12 years later when metastases to the rib and pleura appeared, and the patient died within six months.

Case 13.—A. H., female, age 45, complained of persistent pain and swelling following a sharp blow received from a box falling on the dorsum of the left foot in 1922. An incisional biopsy was made three months later. The wound did not heal, and an amputation through the lower leg was performed one month thereafter. Pathologic examination showed an expansile tumor replacing the proximal four-fifths of the first metatarsal, made up of average malignant cells. Five years and four months later, metastasis appeared in the venous thrombi of the groin. A fungating mass was excised four months later, but the patient died at the end of two weeks from secondary hemorrhage.

Case 14.—C. G., male, age 59, noticed a slowly growing tumor in the upper aspect of the right thigh in 1925, or four years after a fracture of the right hip. When he presented himself at the Memorial Hospital, five years later, the tumor measured at least 13 cm. in diameter. Aspiration biopsy revealed atypical cartilage cells, suggestive of a low-grade chondrosarcoma. No evidence of Paget's disease was noted. About 500 tissue dose (175 K.V.) was delivered to the tumor, and smaller doses repeated four and seven months later. The tumor remained unchanged in size, but three years later local pain developed and the patient died in another hospital from inanition and bronchopneumonia, six years after radiation.

Case 15.—B.S.R. No. 1497: J. S., female, age 14, developed a painful swelling in the lower third of the right femur which, in 1932, or two months after onset, was partially excised. A midthigh amputation was performed one month later. Microscopic and roentgenologic examination showed the tumor to be composed of spindle cells of average malignancy, with little bone formation. Pulmonary metastases appeared five and three-quarters years later, but death did not follow for another year.

Case 16.—L. C., female, age 27, had pleuritic pains and febrile episodes in 1932, which were followed two years later by the appearance of a mass in the left axilla, and loss of 30 pounds in weight. Roentgenologic examination revealed a large tumor involving the third rib and obscuring the left upper lobe of the lung. This, on aspiration biopsy, proved to be an osteogenic sarcoma. Heavy radiation (700 K.V.) apparently imposed growth restraint. Two years later, an exophthalmic goiter was subtotally removed. Five and one-half years after therapy, involvement of the adjacent ribs became apparent and the patient died from extension of the disease within the chest.

SUMMARY AND CONCLUSIONS

A series of 160 histologically proven cases of osteogenic sarcoma treated between 1917 and 1933, at the Memorial Hospital, New York, has been studied from the standpoint of prognosis. In our opinion, the following factors have seemed to influence the outcome:

(1) *Age.*—The prospect of five-year survival is most favorable in patients whose ages range from 20 to 40 years, and least favorable in those who are in the first decade or have passed through the fourth decade of life. Osteogenic sarcoma on a Paget's disease basis gives an extremely bad prognosis; these cases are usually found in the fifth, sixth and seventh decades.

(2) *Sex.*—In our series the survival rate for females is 28 per cent,

whereas that for males is 18 per cent—for which difference we are unable to account.

(3) *Location.*—In bones of an extremity, the more peripheral the lesion, the more favorable the outlook. There were no five-year survivals where the middle or upper femur was the site of disease.

(4) *Pathology.*—A histologic grading of a tumor is of much value in estimating the outcome. Those of low-grade malignancy showed 40 per cent five-year survivals; those of intermediate, 16 per cent; and those of high-grade, 15 per cent.

(5) *Site of Amputation.*—This was of interest to us because 35 per cent of the cases in which amputation was performed through the bone primarily involved, survived five years; whereas only 21 per cent survived amputation by disarticulation of the joint above, and 36 per cent survived amputation through the bone above. Although some authors maintain that one should never amputate through the bone primarily involved, our figures would indicate that for at least low femur tumors, indiscriminate hip-disarticulation was scarcely justified.

(6) Amputation alone or with preoperative conservative surgery (in exceptional cases), or with preoperative radiation, apparently remains the method of choice. It gave a 32 per cent survival (Table VI).

(7) Radiation alone was used in 35 cases, with three survivals, or 9 per cent. It seems unjustifiable to rely on this method alone unless the condition is inoperable or unless operation is refused.

(8) The five-year survival rate based on the *determinate* group (35 cases) was 22 per cent.

We wish to express our very great appreciation of the assistance rendered in this study by Dr. Fred W. Stewart, Pathologist of the Memorial Hospital.

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MEMOIR

WILLIAM DAVID HAGGARD

1872–1940

IN THE DEATH of William David Haggard the surgical profession has lost a shining light, the American Surgical Association mourns a distinguished Fellow and his colleagues are deprived of a genial companion. If what is called "personality" counts for much in this world—and we must believe it does—the subject of this Memoir scores a high mark in the estimation of all those who knew him. It is difficult for one so intimate with him as the writer to put down in mere words a full, just and impartial tribute to this friend and associate over a period of 39 years. On the one hand, there is the temptation to paint the picture in too glowing colors, a natural tendency in a devoted compeer; on the other hand, a certain restraint impels the withholding of those expressions of the inner feelings, still saddened by a grievous loss.

William David Haggard was born in Nashville, Tennessee, September 28, 1872. In order to appreciate his qualities and to evaluate his career it is well to indicate his origin and his associations. His father, Dr. William David Haggard, Sr., a Kentuckian by birth, received his degree from the Jefferson Medical College of Philadelphia in 1851, practiced medicine for 24 years in Gallatin, Tennessee, and removed to Nashville in 1875. At once, he showed interest in medical education, becoming an assistant to the chair of gynecology in the Medical Department of the University of Nashville and Vanderbilt University, and was among the first in the South to accentuate the value of clinical teaching. In 1884, he was chosen as professor of gynecology and diseases of children in the University of Tennessee Medical Department, which had been established some years earlier by Paul F. Eve and W. K. Bowling.

The elder Haggard was a leader of his profession. As a teacher, for nearly a quarter of a century, he made a wholesome and ineffable impression upon the ambitions and practices of hundreds of young medical men throughout the South and West. He continued to fill his chair until his death. Higher standards of medical education found in him an early champion. The Southern Medical College Association selected him as its first president, and rapidly followed the example of the more wealthy colleges of the East in requiring a three- and then a four-years' graded course. He has the distinction of being the first president of the Southern Surgical and Gynecological Association, organized in 1887, and now known as the Southern Surgical Association.

The son followed in the footsteps of his father. He was graduated with first honors from the Medical School of the University of Tennessee in 1893.

Having served a term in the Woman's Hospital of New York, he returned to Nashville, became assistant to his father who conducted a private hospital, and, in 1901, following the death of his father, was advanced from associate

WILLIAM DAVID HAGGARD, M.D.

to the professorship of gynecology and abdominal surgery at his alma mater. In this position he continued until 1912, when the school was removed to Memphis. He was then elected professor of surgery and clinical surgery in the Vanderbilt University School of Medicine, which post he held at the time of his death, January 28, 1940.

To recount the various honors received, positions held, and offices per-

formed by Doctor Haggard is but to assert that in every organization, institution and establishment with which he was connected he went to the top. His capacity for leadership, for executive ability, for doing his own work well and inducing others to work with him was universally acknowledged. In professional circles he was the head of most of the associations to which he belonged—city, county, state, interstate, regional and national. Following is the list of organized medical societies over which, at one time or another, he presided: Nashville Academy of Medicine; Middle Tennessee Medical Association; Tennessee State Medical Association; Southeastern Surgical Congress; Southern Surgical Association; Inter-state Postgraduate Assembly; American College of Surgeons; American Medical Association. He held lesser offices in several of these organizations and was a member of many others. Of these may be mentioned the Society of Clinical Surgery, Pan American Medical Congress, International Society of Surgery. His Fellowship in the American Surgical Association began in 1916, continuing unabated, and with regular attendance, until his death, a period of nearly 24 years. In 1938 he was made a Senior Fellow.

In 1898, Doctor Haggard was married to Miss Mary Laura Champe, of Nashville, who died in 1920. Six years later he married Miss Lucille Holman, also of Nashville, who survived but six years. His children are three—a daughter, Mrs. Burgess Askew, Jr., and two sons, William David III, age 13 and John Holman, 11.

Doctor Haggard was a prolific writer and speaker. His best known collections are "The Romance of Medicine and Other Addresses" and "Surgery—Queen of the Arts, and Other Papers," both headed by the presidential addresses delivered before the two largest professional organizations in America. In addition, he was the author of numerous papers, dealing chiefly with goiter, surgery of the stomach and colon, and appendicitis.

His military record, familiar to his colleagues in World War No. 1, included: Chairmanship of the Medical Section, Council of National Defense for Tennessee and medical aide to the governor; member of the Advisory Board, with rank of major. In the Surgeon General's office, Washington: Consulting surgeon, with rank of lieutenant colonel, M.C. U. S. Army, A.E.F.; and surgeon, Evacuation Hospital No. 1, Toule, France, 1918-1919.

In his community relations Doctor Haggard was also a leader. He was president of his civic and social clubs, received the cup as the most eminent citizen, engaged in many enterprises for the improvement of his native city, won prizes at horse shows, served as an official in his church and was awarded the degree of D.C.L. by the University of the South (Sewanee). On two occasions, when Doctor Haggard had received the highest acclaim of his profession, he was greeted at home by his colleagues and fellow citizens who honored him by public demonstrations and official dinners, when he was given meeds of praise which were his due. Following his death memorial exercises were held by the Nashville Academy of Medicine and the Tennessee Medical Association.

This recital of beginnings, duties and achievements does not begin to tell the story. It is not an overstatement to say that "Will" Haggard personally knew, and was known by, more medical men than any physician of his day and time. His companionable qualities, together with his regular attendance upon the sessions of the numerous societies which claimed him as a member, brought him into the closest association with his colleagues. A ready response to acquaintance was his gift and he never forgot a name or a face. To meet him was to know him, and to know him was to be attracted to him. He was a friendly friend—gay, genial and generous. Not once did he fail to avow an obligation or to grant a favor. His friendship was of the type that began when first formed, carried on with the same understanding whether contacts were rare or frequent, and blossomed forth in joyous fellowship whenever he communed with his comrades. On the surface there appeared only a care-free manner, a hail-fellow-well-met ardor; but deep down inside there were real affection, loyal love for his "buddies" and strong ties of unwavering cordiality. His intimates were few, but to them he manifested at times a serious vein not unmixed even with heartfelt emotion.

As a man, "Will" Haggard was the life of every company in which he found himself. As expressed by Dr. Joseph F. Gallagher, one of his confreres: "Whether he was among the highest or the lowest of the low, he was, despite his stature, a commanding figure." And further: "His art of conversation linked with a gift of repartee and sense of humor, made an impression . . . not easily forgotten. He loved the beautiful, the elegant, and everything that he attempted was done in the manner grand." In the words of Dr. Frank K. Boland, one of our own Fellows: "Truly he did a lot of living in his 67 years. No man ever had more fun or contributed more pleasure to others, nor has one among us worked harder or given more of himself to his profession and to his patients. He leaves a fine example for posterity of happily rounded, beneficent manhood." He is sorely missed; and he will be missed much more as time goes on, when we meet each year and find his place vacant.

As a surgeon, Doctor Haggard possessed those attributes which make for success. Cheerfulness, courage, and humanity marked every step of his life. He showed sound judgment, a tolerant attitude and a progressive disposition. He learned more and more every year by study and observation, and he kept up, aggressively, with the advances in surgery. He believed in the unity of medicine and his experience made him well-rounded in his views of every situation that confronted him. His operative skill was characterized by resourcefulness and quick thinking; he had by nature a manual dexterity which was as gentle and graceful as it was effective. His one idea was to cure the patient by the safest and simplest method. As a clinical teacher he excelled, what with his aptitude of expression combined with a wealth of illustrations and anecdotes.

The end crowns the work. He always dreaded and feared that, in the

ill-health of his latter days, he would succumb to a lingering disease, which would consign him to a period of chronic invalidism. He wanted to leave this world as his friends knew him, the embodiment of physical activity and irresistible enthusiasm. His wish was fulfilled.

According to a newspaper account Doctor Haggard had recently gone to Florida where he had spent a brief vacation with his two sons just before Christmas, and was with a group of Nashvillians at The Breakers Hotel, Palm Beach. He had dined with them Saturday night and appeared in his usual good health. He did not come down to breakfast Sunday morning, and about noon his room was entered and he was discovered dead. Physicians who were called estimated that he had died of a heart attack about seven hours earlier. "He died not too close to the sunset of life, so that the lengthening shadows of his unusual talents and individuality were plain to view and not obscured by the gathering dusk of a falling night of mental darkness. Thus the memory of him by those he loved, and was loved, lives in happy and undying remembrance." (Doctor Gallagher.)

A fitting close for this tribute to our deceased Fellow is contained in a Memoir of his father written in 1901, demonstrating how true to form was the influence of sire upon son: "His only fear in life was of paralysis and a lingering death. He feared that his great physical vigor would postpone the end to a wearying length. He was spared this fear and rewarded with the sudden demise for which he wished—from cerebral hemorrhage."

HUBERT A. ROYSTER, M.D.

BOOK REVIEWS

OPERATIVE SURGERY. By J. SHELTON HORSLEY, M.D., LL.D., F.A.C.S., Richmond, Va., and ISAAC BIGGER, M.D., Richmond, Va. St. Louis, Mo.: C. V. Mosby Co.

THIS is the Fifth Edition of a standard textbook of "Operative Surgery" by Doctors Horsley and Bigger, which was first published in 1921. But three years have elapsed since the appearance of the Fourth Edition; however, no one will take issue with the authors' statement that such rapid progress is now taking place in surgery that a revision at this time was indicated. As in the Fourth Edition, the book appears in two volumes, which are a credit to the publisher and add new laurels to the illustrator, Helen Lorraine.

In the preface one finds outlined the newer procedures which have been added, such as ligation of the patent ductus arteriosus, segmental pneumonectomy, and extrapleural pneumothorax. But this does not speak of the careful reediting which is evident upon almost every page of the book when one compares it with the previous edition.

The chapter on peritonitis has been almost completely rewritten and now occupies 28 pages, and there has been a similar editing of the chapter on appendicitis, which is very greatly expanded.

In this work they still carry a section on orthopedics, which is gradually being deleted from the textbooks on general surgery, and while it maintains its former high standard, the accepted technics of practically all the newer procedures in orthopedic surgery are now included.

The illustrations throughout the entire book maintain the uniform perfection which has been so characteristic of this textbook from its First Edition, and these illustrations are a great asset to those of us who are more visually minded than word minded.

That the authors have accomplished their objective, and have brought this long recognized standard textbook of "Operative Surgery" up to date will be evident to any one fortunate enough to possess a copy.

All concerned in the reediting of this work are to be congratulated upon this addition to our surgical literature. WALTER ESTELL LEE, M.D.

PRINCIPLES OF SURGICAL CARE, SHOCK AND OTHER PROCEDURES. By ALFRED BLALOCK, M.D., Nashville, Tenn. St. Louis, Mo.: C. V. Mosby Co., 1940.

THIS MONOGRAPH is an amplification of the Beaumont Lecture, delivered, in 1940, by the author, under the auspices of the Wayne County Medical Society of Michigan, and serves to continue, uninterruptedly, the series of physiologic monographs inaugurated in 1922, as a tribute to William Beaumont.

As stated in the preface, the author's purpose is to present a discussion of the principles involved in these problems instead of a didactic and detailed consideration of the preoperative and postoperative treatment of surgical patients. To the reviewer, he has fully succeeded in his main objective, which was to emphasize the fact that the operation is only a part of the treatment of surgical patients, and that the recent decrease in the morbidity and mortality rates is due more to advances in preoperative and postoperative treatment than to any other factor. A far cry from the epigram credited to Larry: "I make the wounds, God heals them."

It is now realized that it is inadequate to discuss the subject of shock without considering such etiologic factors as dehydration, hypoproteinemia, acid-base disturbances, *etc.*, but the clinical importance of these changes extends far beyond the production of shock, so that the amount of text which the author devotes to these etiologic and associated factors is much greater than that given to the subject of shock. The general reference to his many associates removes any possibility of criticism of insularism, and for the final result the surgical and medical professions are under great obligations.

The catholicity of this book is in contrast with the one recently written by Scudder,

and although they are not in complete agreement, they evidence the careful research which has been made, and is continuing, in an effort to make surgery safer for the patient. Here is a book which should not only be in the library of every surgeon and physician, but its contents should become as much a part of them as their knowledge of Gray's Anatomy and Osler's Medicine.

The author and the publisher are to be congratulated, and the Lectureship Foundation Committee of the Wayne County Medical Society thanked for this remarkable work which they have made available to the medical profession at large.

WALTER ESTELL LEE, M.D.

CANCER OF THE COLON AND RECTUM: ITS DIAGNOSIS AND TREATMENT. By FRED W. RANKIN, M.D., Surgeon, St. Joseph's and Good Samaritan Hospitals, Lexington, Ky., and A. STEPHENS GRAHAM, M.D., Surgeon, Stuart Circle Hospital, Richmond, Va. Springfield, Ill.: Charles C. Thomas Co., 1940.

RANKIN AND GRAHAM, in this book, present their experience with cancer of the lower gastro-intestinal tract, and have tried to correlate their work with that of other surgeons interested in this field, both in this country and abroad. They feel that the reduction in mortality from cancer of the large bowel during the last 25 years is one of the most outstanding surgical accomplishments during that period, and undoubtedly Rankin has contributed as much to this result as any other American surgeon of his generation. He himself feels that the gradual decrease in the mortality is the result of more accurate methods of diagnosis, the meticulous preoperative preparation and postoperative care, together with perfection of surgical technic.

Since the publication, in 1932, of his book on "Diseases of the Colon and Rectum," his technic has been modified in many ways, and particularly in the direction of closer cooperation between internist and surgeon in the management of the patient pre- and postoperatively, which has resulted in an appreciation of the need for preoperative decompression of the large bowel and a rehabilitation of the patient before any operative procedure can be considered.

The authors now feel that, in the past, undue prominence was given to the employment of intraperitoneal vaccine, and they have now abandoned it.

They also pay tribute to the increased efficiency of radiology in recognizing early lesions, and in the more accurate localization of them. This is more than lip service, in that he has allotted a chapter to Doctor Hodges, in which is explained, in a very clear, concise way, the details of this technic and what can be expected from it, both positively and negatively.

The authors are very definite in their present attitude toward two-stage instead of a one-stage operation in obstructive lesions of cancer of the middle and lower colon, and they are convinced that one does a more radical operation and removes wider areas of lymph node-bearing tissue than when primary reestablishment of the continuity of the bowel is attempted. Further, in this type of operative approach, they precede it with a cecostomy in order to decompress the colon. On the other hand, for cancer of the rectum, in the average risk, they now use, almost exclusively, a one-stage, abdomino-perineal procedure instead of a two-stage operation, which was formerly employed.

Thus it will be seen that Rankin's technic is gradually changing, as is that of most of the surgeons engaged in this type of work, and it is interesting to note that there is now more general agreement among them than at any time in the past.

The book is divided into four parts: (1) Preface; (2) general considerations, which include etiology, pathology, symptoms and diagnosis; (3) treatment; and (4) the operative procedures.

With Rankin's vast experience in this field he can speak with authority, and his attitude of encouragement toward the steady improvement in the end-results now being obtained in cancer of the large bowel should be noted with interest.

There is a bibliography at the end of each chapter, and an authors' and a subject index at the end of the book.

WALTER ESTELL LEE, M.D.

FINNEY-HOWELL RESEARCH FOUNDATION, INC.

Announcement has been made by the Finney-Howell Research Foundation, Inc., that all applications for fellowships for next year must be filed in the office of the Foundation, 1211 Cathedral Street, Baltimore, Maryland, by January 1, 1941. Applications received after that date cannot be considered for 1941 awards, which will be made the first of March, 1941.

This Foundation was provided for in the will of the late Dr. George Walker of Baltimore for the support of "research work into the cause or causes and the treatment of cancer." The will directed that the surplus income from the assets of the Foundation together with the principal sum should be expended within a period of ten years to support a number of fellowships in cancer research, each with an annual stipend of two thousand dollars, "in such universities, laboratories and other institutions, wherever situated, as may be approved by the Board of Directors."

Fellowships carrying an annual stipend of $2000 are awarded for a period of one year, with the possibility of renewal up to three years; when deemed wise by the Board of Directors, special grants of limited sums may be made to support the work carried on under a fellowship.

Applications must be made on the blank forms which will be furnished by the Secretary or any member of the Board of Directors.

October 15, 1940

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SULFATHIAZOLE, "Ciba" (2-Sulfanilyl-Aminothiazole) is available in 0.5 gram tablets, in bottles of 50, 100, 500 and 1000. Also available are 5 gram bottles of Sulfathiazole crystals for making solutions to be used as a reagent in estimating the sulfathiazole content of the blood.

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